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The link between prenatal exposure to a chemical mixture, cord blood hormones, and birth weight: an epidemiologic study

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ABSTRACT

Prenatal chemical exposure has frequently been associated with fetal growth, although the underlying molecular mechanisms remain unclear. This study aims to explore the potential mediating role of hormones in the association between prenatal chemical mixture exposure and birth weight.

We used data of 432 newborns from two Flemish birth cohorts. The common set of available and detectable exposure biomarkers and hormones analyzed in cord plasma are: 6 metals/trace elements, 3 polychlorinated biphenyl (PCB) congeners, hexachlorobenzene, dichlorodiphenyldichloroethylene and 2 perfluoroalkyl substances; and 3 thyroid, 3 reproductive and 2 metabolic hormones. Mixtures analyses were performed to assess each of the bilateral associations in the path exposures-hormones-birth weight, including mediation analysis.

Combining all exposures, we found an inverse association between PCB 180 and birth weight. PCB 180 was positively associated with sex hormone-binding globulin (SHBG) and negatively associated with leptin and insulin. Similarly, thallium was positively associated with testosterone, estradiol, and SHBG, and negatively with insulin. Lead was positively associated with insulin. Higher free thyroxine (FT4), insulin, and leptin were associated with higher birth weight, whereas higher SHBG was associated with lower birth weight. Mediation analysis for PCB 180 indicated that 94% of the effect of this exposure on birth weight is mediated by FT4, SHBG, leptin, and insulin.

Assessing the health risk of chemical mixture exposure reflects better real-world situations, thereby allowing more effective risk assessment. Our results suggest that hormonal markers are on the causal path in the association between environmental exposure and birth weight, adding interesting insights for mechanistic research.

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1. Introduction

Across Europe, 1 in 15 babies (6.6 %) are born with low birth weight (LBW), defined in a clinical setting as a birth weight of less than 2500 g (Ohuma et al., 2023). The leading causes of LBW are intrauterine growth restriction (IUGR), also known as fetal growth restriction, and preterm birth (PTB), which means a gestation period below 37 weeks. LBW is the leading cause of mortality in children under 5 years worldwide (Cutland et al., 2017; Ohuma et al., 2023). Reduced fetal growth is considered a public health indicator of maternal health, nutrition, and poverty, but it is also a predictor of neurologic disability, impaired language and academic development, and a risk factor for chronic diseases such as diabetes and cardiovascular diseases (Cutland et al., 2017). Ensuring healthy intrauterine development is therefore of prime importance for the lifelong health of humans.

Some environmental chemical pollutants may affect fetal growth through IUGR and PTB (Anil et al., 2020; Street & Bernasconi, 2020). Although there are many epidemiological studies that assessed the impact of chemical pollutants on birth outcomes, they often show inconsistent results. For instance, prenatal per- and polyfluoroalkyl substances (PFAS) exposure has been associated with lower birth weight (Zhang et al., 2023), while organophosphate ester flame retardants (OPFRs) showed associations towards greater fetal growth (Oh et al., 2024). Research on polychlorinated biphenyls (PCBs) has produced mixed results, with some studies reporting unclear associations or a negative correlation between PCB exposure and birth weight (Longnecker et al., 2005; Zou et al., 2019). For metals, several studies have found that higher cadmium levels were associated with reduced fetal growth (Guo et al., 2017; Kippler et al., 2012).

The identification of mediating biological pathways linking chemical mixtures exposure to birth outcomes, is important for early detection of disease and prevention and can strengthen causal interpretation of exposure-effect associations in epidemiologic studies. Experimental research has reported alterations in hormonal homeostasis as a plausible biological mechanism for the effects of PCBs and dichlorodiphenyldichloroethylene (DDE) on birth weight (Wang et al., 2005), suggesting that hormones play a key role in causing this effect. Several endocrine disrupting chemicals (EDCs), particularly those with estrogenic activity, are suspected to disrupt the programming of endocrine signaling pathways during development (Newbold, 2011). Estrogen has an important role in regulating the developmental processes required for placental vascularization and fetal follicular maturation (Albrecht & Pepe, 2010). Other proposed endocrine disrupting mechanisms are changes in glucocorticoids and other steroid hormones that may affect neuronal circuits involved in energy balance regulation (Harris & Seckl, 2011). The exact target tissue is unknown and probably involves multiple target sites, e.g., adipocytes, brain, liver, stomach, or pancreas; and the effects may be age, dose, and sex dependent. Moreover, EDCs interfere with thyroid hormone function by interacting with the hypothalamus-pituitary-thyroid (HPT) axis (Thambirajah et al., 2022). In a recent review, PCB exposure was associated with hypothyroidism in rodents, fish, and chicken embryos (Mohammadparast-Tabas et al., 2023). Another review suggested that PFAS altered thyroid hormones, thyroid hormone gene expression, and histology, which are associated in animal studies with decreased body and organ weight (Gundacker et al., 2022). Mediation through estrogenic and thyroid hormones was also confirmed in two human epidemiological studies in which the observed association between PFAS and fetal growth seemed to be mediated by estrogens (Wang et al., 2019) and thyroid-stimulating hormone (TSH) (Wang et al., 2023). Moreover, fetal thyroid, reproductive and metabolic hormone levels are reported to be associated with fetal growth (Al-Omary & Alawad, 2019; Shields et al., 2011a; Wang et al., 2020).

Much of the existing epidemiological evidence examined the impact of single exposures, not reflecting real-life situations where people are exposed to mixtures of several chemical substances, which might have additive, antagonistic or synergistic effects. Single-pollutant analyses also ignore potential confounding by other substances in the mixture and do not account for potential mixture compositions in which the presence of certain compounds may determine the activity of others. Therefore, the focus of health impact assessments of environmental exposures has shifted to multiple-pollutant approaches in recent years, and the field of statistical tools suited for this purpose has evolved accordingly (Zhu et al., 2024). Likewise, when multiple correlated effect biomarkers are operating on the same causal pathway, the use of traditional single-mediator analysis for each biomarker can be problematic since the resulting estimates may be biased because confounding by mediators is not included in the model (Clark-Boucher et al., 2023). Exploiting the joint multivariable structure reduces the risk of bias and increases precision, so using a multiple-mediator model including all relevant mediators is recommended.

In this study, we aimed to assess the potential mediating role of selected molecular biomarkers (thyroid, reproductive, and metabolic hormones) in the relation between prenatal chemical mixture exposure and birth weight by pooling data from two Flemish birth cohorts. This allowed us to examine the molecular-based mechanisms underlying the effect of EDCs on fetal growth.

2. Material and methods

2.1. Study population

The Flemish Environment and Health Studies (FLEHS) program is a consecutive cycle of HBM studies conducted every 4–5 years. This study used data from two successive cycles, FLEHS II (2007–2011) and III (2012–2015) in newborns. FLEHS II and III participants were recruited from the five Flemish provinces' general population between 2008–2009 and 2013–2014 respectively, using a two-stage sampling procedure with provinces as primary sampling unit and maternities as secondary sampling units. The distribution of participants over the different provinces was proportional to the number of inhabitants in that province. More details on the recruitment have been published before (Baeyens et al., 2014; De Craemer et al., 2017). In total, 255 and 281 mother-newborn pairs were obtained from FLEHS II and III respectively. All mothers signed an informed consent. Inclusion criteria were the ability to fill out a Dutch questionnaire and to live at least 10 years in Flanders (FLEHS II) or at least five years in Flanders (FLEHS III). The human biomonitoring studies were approved by the Ethical Committee of the University of Antwerp and the University Hospital of Antwerp and the Ethical Committees of the local hospitals if this was demanded by the local hospital rules.

The study population was restricted to live-born singleton births, with available measurements of the outcome (birth weight), selected exposure markers and hormones, and *a priori* selected covariates. Birth weight was recorded shortly after delivery, together with the covariates gestational age (weeks) and sex of the newborn (male/female). Other covariate data were obtained from the questionnaires and categorized as follows: maternal age at delivery (<27, 27 < 30, 30 < 33, ≥33 years), maternal pre-pregnancy body mass index (BMI: <18.5 kg/m^2 = underweight, 18.5–24.9 kg/m^2 = normal weight, 25–29.9 kg/m^2 = overweight, ≥30 kg/m^2 = obese), parity (0, 1, ≥2) and maternal smoking during pregnancy (nonsmoking, smoking). Study cycle was included as an additional covariate. After excluding non-singletons (n = 7), observations with missing covariate information (n = 5 for gestational age, n = 2 for maternal pre-pregnancy BMI, n = 1 for parity, n = 6 for maternal smoking), observations without exposure biomarker measurements (n = 6 for metals, n = 7 for PCBs and chlorinated pesticides, n = 47 for PFAS), 1 observation without lipid measurement (used for standardization of PCBs and chlorinated pesticides, see further), and observations without effect biomarker measurements (n = 15 for thyroid hormones, n = 21 for testosterone and sex hormone-binding globulin, n = 30 for total estradiol, n = 1 for insulin), 432 mother-newborn pairs (164 from FLEHS II, 268 from FLEHS III) were available for further analyses.

2.2. Quantification of hormones

Thyroid hormones (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], free thyroxine [FT4], reproductive hormones (total testosterone [T], total estradiol [E2], sex hormone-binding globulin [SHBG], follicle-stimulating hormone [FSH], luteinizing hormone [LH]), and metabolic hormones (insulin [INSU], leptin [LEPT]) were measured in cord blood plasma. Cord blood samples were collected by the midwife and processed according to centrally developed guidelines, either by the hospital laboratory, or by an associated external routine laboratory. Plasma samples were centrifuged; cord blood and plasma samples were aliquoted in the appropriate tubes and stored at −20 °C until transport to the central laboratory. Samples were frozen within 6 h (FLEHS II) or 24 h (FLEHS III) after collection. In the central laboratory samples were stored at −80 °C. After completion of the recruitment period, all the samples, together with field blanks and control samples, were transported from the central lab to the different analytical laboratories, for which University of Ghent (FLEHS II: thyroid & reproductive hormones) and A.M.L laboratory (Antwerp, Belgium) (FLEHS II: metabolic hormones; FLEHS III: all hormones) performed the effect biomarker analyses. Commercial immunoassays were used to determine plasma levels of the reproductive hormones. The thyroid hormones FT3, FT4 and TSH were determined by direct chemiluminescent immunoassays. The metabolic hormones LEPT and INSU were measured by A.M.L for both FLEHS II and III. In FLEHS II, LEPT was quantified using ELISA, and in FLEHS III a radio-immunoassay was used. INSU was measured using an immunoradiometric assay (IRMA) in FLEHS II, and a chemiluminescent microparticle immunoassay in FLEHS III. Details on analytical method and assays used, as well as quality control information can be found in Supplementary Table S1. Only the biomarkers that were detected in at least 50 % of the samples in both study cycles were considered, resulting in the exclusion of FSH (4 % below limit of detection (LOD) of 0.1 IU/L in FLEHS II, 75 % below limit of quantification (LOQ) of 0.3 IU/L in FLEHS III) and LH (59 % below LOD of 0.1 IU/L in FLEHS II, 70 % below LOQ of 0.3 IU/L in FLEHS III) from further analyses. Resulting in 8 hormones that were included for further analysis. In FLEHS II the LOD was reported as cut-off to report quantifiable data and to calculate the detection frequency, while in FLEHS III only the LOQ was reported.

2.3. Exposure assessment

For this study, we selected all exposure biomarkers that were measured in both FLEHS cycles and that were detected in at least 50 % of the samples within each cycle, resulting in a total of 13 exposure biomarkers that were available for further statistical analysis: (a) six metals/trace elements, including cadmium (Cd), lead (Pb), total arsenic (As), copper (Cu), manganese (Mn), and thallium (Tl); (b) three PCBs, including PCB 138, 153, and 180; (c) two chlorinated pesticides, including hexachlorobenzene (HCB) and dichlorodiphenyldichloroethylene (DDE); (d) two PFAS, including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). Exposure biomarkers measured in both cycles that did not meet this criterion were some additional PCBs (99, 105, 118, 170, 187) and some polybrominated diphenyl ethers (BDE 28, 47, 99, 100, 153, 154, 183). Metals and trace elements were measured in cord blood by High Resolution Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS) (Schroijen et al., 2008). PCBs and chlorinated pesticides were measured in cord plasma by gas chromatography-electron capture negative ionization mass spectrometry (GC-ECNI/MS) (Covaci & Voorspoels, 2005). PFAS were measured in cord plasma by high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) (Colles et al., 2020). Overview of analytical method used, as well as quality control information can be found in Supplementary Table S1. Although measurements in the two studies were performed by the same analytical methods and by the same laboratories of the Free University of Brussels (metals), University of Antwerp (PCBs and chlorinated pesticides) and University of Aachen (PFAS), these methods were improved over time resulting in lower LOQs for all exposure biomarkers, except As and DDE (Supplementary Table S2). PCBs and chlorinated pesticides were standardized by total lipid concentration. Lipids were determined by enzymatic methods, and lipid adjustment of organochlorines was based on total lipids as calculated according to the formula obtained in FLEHS I, based on the measurement of cholesterol and triglycerides: total lipids = 50.49 + 1.32 × (cholesterol + triglycerides) in mg/dL (Schoeters et al., 2017).

2.4. Statistical methods

Within each study cycle, exposure biomarkers and hormone concentrations below the LOD or LOQ (depending on what was reported by the laboratory) were imputed by single random imputation from a censored log-normal probability distribution (Lubin et al., 2004). Assuming the data is log-normally distributed and left-censored, a lognormal distribution was fitted to the censored data using maximum likelihood estimation. Each censored data point was then substituted by a value between zero and the LOD/LOQ sampled from the fitted lognormal distribution. Although this method ignores the uncertainty in imputed values, it is expected to provide a relatively unbiased estimate of the average of the biomarker level, particularly when the percentage of censoring is not high. For most of the included exposure biomarkers the percentage of imputed values was neglectable (<4%), except for Cd, PCB 138, and PCB 180 in FLEHS II (32 %, 17 %, and 20 % respectively), and HCB in both study cycles (49 % and 21 % respectively) (Supplementary Table S2). Differences in population characteristics, exposure biomarkers, and effect biomarker concentrations between FLEHS cycles were assessed by chi-square tests (categorical variables), analysis of variance (birth weight and gestational age), or Kruskal-Wallis tests (exposure and effect biomarkers). Exposure and effect biomarkers were ln-transformed before further statistical analyses. Exposure biomarkers were only scaled (divided by their standard deviation), whereas effect biomarkers were centered within study cycle (to adjust for differences which are linked to the different measurement methods used in the two cycles) and then scaled across study cycles. As a sensitivity analysis, stratified analyses by study (FLEHS II and III) were performed. Correlations between exposure biomarkers and correlations between effect biomarkers were calculated using Pearson correlations on the ln-transformed concentrations. The high correlation between PCB 138, PCB 153, and PCB 180 (>0.8) resulted in multicollinearity: the inclusion of the 3 PCBs in the same multiple linear regression model for birth weight produced elevated variance inflation factors (2.5, 4.2, and 3.4 for PCB 138, PCB 153, and PCB 180, respectively) and reversed the sign of regression coefficients for PCB 138 and PCB 180 compared to coefficients obtained from models including only the single PCBs. Therefore, only PCB 180 was included in statistical models, as this PCB congener was found to be most consistently associated with birth weight in our previous study (Govarts et al., 2020). Eleven exposure biomarkers were included in further analyses.

In a first analysis, the following associations were examined: (1) the associations between exposure biomarkers and birth weight; (2) the associations between hormones and birth weight, and (3) the associations between exposure biomarkers and hormones. We used three "mixture" approaches in which the effect of multiple exposure biomarkers or multiple hormones were assessed in the same model: multiple linear regression (MLR), Bayesian kernel machine regression (BKMR) (Bobb et al., 2015) and Bayesian model averaging (BMA) (Clyde et al., 2011).

BKMR is a non-parametric method that models the mixture response using a kernel function that considers potential interactions between mixture components and a possible nonlinear association between mixture components and the outcome (Bobb et al., 2018). A Markov Chain Monte Carlo (MCMC) algorithm is used to estimate model

parameters. Variable importance for mixture components is usually based on inspecting posterior inclusion probabilities (PIPs). The PIP is the proportion of MCMC iterations in which a mixture component (in case of component-wise variable selection) or group of components (in case of hierarchical variable selection) was selected into the model. The median probability model, which consists of those variables whose PIP is at least 0.5, is often the optimal predictive model, so a PIP threshold of 0.5 or higher is typically used as a cut-off for variable selection (Barbieri & Berger, 2004). In this study we used component-wise variable selection and the default Gaussian kernel function. In our experience, the algorithm used to fit the BKMR model may struggle to converge in the presence of strongly correlated exposures, and we therefore fitted the model using relatively many iterations (50,000 instead of the default 10,000) and using four parallel MCMC chains to allow more detailed diagnosis of model convergence. Models were fit using the bkmr and bkmrhat packages in R (Bobb et al., 2018).

For BMA, we used the Bayesian adaptive sampling (BAS) algorithm described in Clyde et al. (Clyde et al., 2011). Unlike MCMC, BAS is guaranteed to enumerate the space of models if the number of iterations is equal to the dimension of the model space, but uses a stochastic sampling algorithm when enumeration is not feasible (Clyde et al., 2011). We used 50,000 iterations and calculated the PIP for each mixture component using the posterior sampling probabilities for each model in which they were included (Barbieri & Berger, 2004). The R package BAS was used to implement the analysis, using the Jeffreys-Zellner-Siow prior for the regression coefficients and a uniform (flat) prior on the model space (Liang et al., 2008). Estimates and 95 % Bayesian credible intervals were obtained using the full posterior distribution of all regression coefficients. When no strong evidence for nonlinearity or interaction effects was found in BKMR models, BMA was considered to be the main model for interpretation of results (Bobb et al., 2018; Bürkner, 2017; Carpenter et al., 2017; Piironen & Vehtari, 2017; Zou & Hastie, 2005).

All of the above models were adjusted for cord blood cholesterol (which is a precursor for many of the studied hormones), gestational age (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy, and study cycle (Delcroix et al., 2023; Fall et al., 2015; Hinkle et al., 2014; Liu et al., 2022; Love & Kinch, 1965; Sharma, 2023; Wilcox & Skjaerven, 1992). Together with maternal diabetes and (thyroid, sex, and metabolic) hormones, these variables were identified as the minimal sufficient adjustment set for estimating the direct effect of prenatal mixture exposure on birth weight, based on the Directed Acyclic Graph (DAG) presented in Supplementary Fig. S1 (created using the DAGitty tool version 3.1). Because of the low number of maternal diabetes cases ($n = 8$), we did not adjust for this variable but excluded the maternal diabetes cases in a sensitivity analysis. Cholesterol was excluded as covariate in another sensitivity analysis. Covariates were forced into BKMR and BMA models by including them in the minimal model.

In a second analysis, we applied causal mediation analysis to examine the role of hormones as potential mediators in the pathway between exposure biomarkers and birth weight. Mediation analysis was only done for exposure biomarkers which were found to be associated with birth weight and at least one of the hormones of interest. As this was only the case for PCB 180, mediation analyses were restricted to single-exposure single-mediator and single-exposure multiple-mediator models. A significant total effect (between exposure and birth weight) is not a strict criterion for the presence of mediation, because non-significant total effects may also occur: (1) when direct and indirect effects are in opposite directions and cancel each other out, or (2) when the sizes of both direct and indirect effects are small, resulting in a lack of power (MacKinnon et al., 2007). In this study, we did not assess potential mediation for exposures that lacked a significant total effect to lower the risk of false positives. In single- and multiple-mediator analyses, outcome and mediator models were adjusted for the same covariates as included in the first set of analyses, whereas mediator models were additionally adjusted for exposures that may confound the PCB 180 – hormone associations, i.e., exposures that were found to be associated with the hormones in the mixture – hormone analysis.

Single-mediator analysis was performed using the R package "mediation" (Tingley et al., 2014), fitting the following linear regression models: (1) the outcome model which estimates the effect of the exposure biomarker (β_a) and the hormone (β_m) on birth weight, and (2) the mediator model which estimates the effect of the exposure biomarker on the hormone (α_a). The direct effect of the exposure biomarker on birth weight was estimated by β_a, and the indirect (mediation) effect by $\alpha_a{*}\beta_m$. The proportion of mediation was calculated as the ratio of the indirect effect to the total effect multiplied by 100. The statistical significance of these estimates was obtained by quasi-Bayesian approximation with (the default setting of) 1000 Monte Carlo draws.

Multiple-mediator analysis was performed by the high dimensional mediation analysis (HDMA) method proposed by Gao et al. (2019), using the hdmed package in R (Clark-Boucher et al., 2023). HDMA is a penalized regression approach that includes a feature selection step for the potential mediators in the outcome model. In a first step, the outcome model is fit with the de-sparsified LASSO (Zhang & Zhang, 2014). Penalized estimators are typically biased and cannot be directly used for testing or confidence interval construction. The de-sparsified LASSO method tries/aims to solve this issue by implementing a debiasing technique which accounts for correlations between variables and produces bias-corrected estimates which are asymptotically normally distributed, allowing for simultaneous estimation and significance testing of regression coefficients. In a second step, the mediator models are fit, applying ordinary linear regression to the mediators selected by the outcome model (P-value < 0.05).

Estimated regression coefficients are presented as the change in mean birth weight (g) or the ratio of the geometric mean hormone concentrations (further referred to as geometric mean ratio) for an interquartile fold change in exposure or hormone concentrations (IQFc; the fold change of the 75th percentile over the 25th percentile), with 95 % confidence intervals (CI) for MLR and 95 % credible intervals (CrI) for BKMR and BMA.

3. Results

Study population characteristics are summarized in Table 1. A total of 432 newborns were included in the analyses, consisting of 212 girls (49.1 %) and 220 boys (50.9 %) with a mean gestational age of 39.3 weeks (range 35–42 weeks) and a mean birth weight of 3465.5 g (range 2175–4950 g). The median maternal age was 29.7 years (range 18–44 years) and 10.6 % of mothers smoked during pregnancy. The mean maternal pre-pregnancy BMI for the pooled sample was 23.7 kg/m^2 (range 15.2–47.4 kg/m^2. BMI in categories differed significantly between cycles, with FLEHS III having a lower percentage of underweight (2.6 % versus 7.3 %) and normal weight (66.4 % versus 71.3 %) mothers, but a higher percentage of overweight mothers (21.3 % versus 12.2 %) than FLEHS II. Consistent with the decreasing time trends observed for many exposures in earlier analyses of the FLEHS data (Schoeters et al., 2017), cord blood concentrations were significantly lower in FLEHS III than in FLEHS II for all exposure biomarkers except for Mn concentrations, for which they were similar, and As, Tl and HCB concentrations, which were significantly higher in FLEHS III (Table 2). Hormone concentrations were significantly lower in FLEHS III than in FLEHS II (probably related to different kits/methods in immunoassays used for hormone measurements), except for SHBG, which did not differ significantly between cycles, and FT3, which was significantly higher in FLEHS III (Table 2).

Pearson correlations between (ln-transformed) exposure biomarkers were mostly low (<0.4), except for the strong correlations (>0.8) between PCB congeners, and some moderate correlations (0.40–0.51) between PCBs and DDE, between PCBs and PFOS, between PFOS and PFOA, and between Cd and Pb, PCBs, and PFOS (Supplementary

Table 1
Characteristics of newborns from the Flemish Environment and Health Studies, Flanders (FLEHS II & III, n = 432).

Characteristic	N (%) or mean (SD)			*P*-value[a]
	FLEHS II	FLEHS III	Total	
Sex				
Female	82 (50.0)	130 (48.5)	212 (49.1)	0.840
Male	82 (50.0)	138 (51.5)	220 (50.9)	
Gestational age (weeks)	39.4 (1.2)	39.3 (1.2)	39.3 (1.2)	0.694
Maternal age at delivery (years)				
<27	34 (20.7)	60 (22.4)	94 (21.8)	0.522
27–29	45 (27.4)	71 (26.5)	116 (26.9)	
30–32	50 (30.5)	67 (25.0)	117 (27.1)	
≥33	35 (21.3)	70 (26.1)	105 (24.3)	
Maternal pre-pregnancy BMI (kg/m²)				
<18.5	12 (7.3)	7 (2.6)	19 (4.4)	0.017
18.5–24.9	117 (71.3)	178 (66.4)	295 (68.3)	
25–29.9	20 (12.2)	57 (21.3)	77 (17.8)	
≥30	15 (9.1)	26 (9.7)	41 (9.5)	
Maternal diabetes				
No	164 (100.0)	260 (97.0)	424 (98.1)	0.062
Yes	0 (0.0)	8 (3.0)	8 (1.9)	
Parity				
0	64 (39.0)	119 (44.4)	183 (42.4)	0.269
1	57 (34.8)	96 (35.8)	153 (35.4)	
≥2	43 (26.2)	53 (19.8)	96 (22.2)	
Maternal smoking during pregnancy				
No	148 (90.2)	238 (88.8)	386 (89.4)	0.757
Yes	16 (9.8)	30 (11.2)	46 (10.6)	
Birth Weight (g)	3491.7 (472.1)	3449.5 (431.4)	3465.5 (447.2)	0.343

[a] *P*-value assessing the difference between study cycles, based on a chi-square test for categorical variables and analysis of variance for continuous variables. Abbreviations: SD, standard deviation; FLEHS, Flemish Environment and Health Study; BMI, body mass index.

Table 2
Exposure and effect biomarkers measured in cord blood of newborns from the Flemish Environment and Health Studies, Flanders (FLEHS II & III, n = 432).

Biomarkers	Median (P25-P75)			*P*-value[a]
	FLEHS II	FLEHS III	Total	
Metals in cord blood (μg/L, except for Tl which is expressed ng/L)				
Cd	0.08 (0.05–0.10)	0.02 (0.02–0.03)	0.03 (0.02–0.06)	<0.001
Pb	8.3 (6.5–11.4)	6.1 (4.9–8.6)	7.2 (5.3–9.8)	<0.001
As	0.5 (0.2–1.2)	0.6 (0.3–1.2)	0.6 (0.3–1.2)	0.026
Cu	587.5 (531.7–667.8)	572.6 (512.4–624.5)	576.0 (519.8–642.7)	0.007
Mn	30.4 (24.4–38.0)	30.2 (24.0–38.1)	30.2 (24.1–38.1)	0.667
Tl	17.0 (14.0–21.0)	18.0 (15.6–22.1)	17.9 (15.0–21.8)	0.013
Polychlorinated biphenyls in cord plasma (ng/g lipid)				
PCB 138	19.8 (14.0–26.3)	10.6 (7.0–16.0)	13.5 (8.7–20.5)	<0.001
PCB 153	29.3 (19.5–39.8)	16.9 (11.5–24.4)	20.7 (13.8–30.8)	<0.001
PCB 180	17.5 (11.8–23.9)	8.7 (5.7–13.1)	11.1 (7.1–18.0)	<0.001
Chlorinated pesticides in cord plasma (ng/g lipid)				
HCB	9.7 (6.7–16.8)	14.7 (6.6–20.8)	12.1 (6.7–19.6)	0.002
DDE	74.2 (49.1–125.7)	55.4 (36.6–89.8)	61.8 (40.0–105.5)	<0.001
Perfluorinated compounds in cord plasma (μg/L)				
PFOA	1.5 (1.1–2.1)	1.3 (0.9–1.6)	1.4 (1.0–1.8)	<0.001
PFOS	2.7 (1.8–3.9)	1.1 (0.7–1.7)	1.5 (0.9–2.6)	<0.001
Effect biomarkers in cord plasma				
TSH (mIU/L)	8.1 (5.7–11.4)	5.7 (4.3–8.3)	6.3 (4.9–9.5)	<0.001
FT3 (pg/mL)	1.5 (1.3–1.6)	1.7 (1.6–1.9)	1.6 (1.5–1.8)	<0.001
FT4 (ng/dL)	1.3 (1.2–1.4)	1.1 (1.0–1.2)	1.2 (1.1–1.3)	<0.001
T (ng/dL)	149.8 (111.5–184.0)	93.5 (77.0–112.2)	107.0 (84.0–138.3)	<0.001
E2 (pg/mL)	7257 (5018–10944)	2605 (1954–3381)	3408 (2366–6924)	<0.001
SHBG (μg/dL)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.775
INSU (mU/L)	5.7 (4.4–7.3)	4.4 (3.0–7.0)	5.0 (3.5–7.2)	<0.001
LEPT (μg/L)	16.8 (10.7–26.6)	5.2 (3.3–9.1)	8.0 (4.2–15.3)	<0.001
CHOL (mg/dL)	69.5 (60.0–82.0)	64.0 (55.0–76.0)	66.0 (56.0–77.2)	0.002

[a] P-value assessing the difference between study cycles based on a Kruskal-Wallis test. Abbreviations: P25, 25th percentile; P75, 75th percentile; FLEHS, Flemish Environment and Health Study; Cd, cadmium; Pb, lead; As, total arsenic; Cu, copper; Mn, manganese; Tl, thallium; PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; DDE, dichlorodiphenyldichloroethylene; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T, testosterone; E2, estradiol; SHBG, sex hormone-binding globulin; INSU, insulin; LEPT, leptin; CHOL, cholesterol.

Fig. S2). Correlations between hormone concentrations were low, except for the correlation between T and E2 (0.55) (Supplementary Fig. S3).

In our previous multiple-pollutant analysis that included 4 birth cohorts, birth weight was negatively associated with PCB 180 and positively with DDE (Govarts et al., 2020). Results from the current analysis (on a smaller sample) also suggested a negative association between PCB 180 and birth weight (Fig. 1, left panel; Supplementary Table S3), although it did not appear to be very strong ($P_{MLR} < 0.05$, $PIP_{BKMR} = 0.47$, $PIP_{BMA} = 0.37$). BKMR results did not show nonlinearity or interactions in the PCB 180-birth weight associations (Supplementary Fig. S4). Estimates for the difference in birth weight per IQFc in PCB 180 ranged from −111 g (95 % CI: −190; −31) in the MLR model to −36 g (95 % CrI: −139; 0) in the BMA model. No association of birth weight with DDE or other exposures was observed.

FT4, INSU, and LEPT were positively associated and SHBG negatively associated with birth weight (PIPs > 0.8, except for $PIP_{BKMR} = 0.73$ for FT4) (Fig. 1, right panel; Supplementary Table S3). The bivariate hormone-birth weight plots (Supplementary Fig. S5) suggested an increase in the slope of the INSU-birth weight association at higher concentrations of LEPT, but there was no evidence for strong interaction effects, nor for nonlinearity in the hormone-birth weight associations. Estimates for the difference in birth weight per IQFc in FT4, INSU, LEPT, and SHBG from the BMA model were 63 g (95 % CrI: 0; 116), 57 g (0; 96), 296 g (229; 364), and −45 g (−79; 0), respectively.

Results of the exposure – hormone analyses (Fig. 2, Supplementary Table S4) suggested a positive association between E2 and Cu (PIPs > 0.8), between E2 and Tl ($PIP_{BKMR} = 0.55$, $PIP_{BMA} = 0.75$) and between T and Tl ($PIP_{BKMR} = 0.79$, $PIP_{BMA} = 0.75$). SHBG was negatively associated with As, and positively with Cu, Tl, and PCB 180 (PIPs > 0.8, except for $PIP_{BKMR} = 0.70$ for As and $PIP_{BKMR} = 0.64$ for PCB 180). INSU was positively associated with Pb, and negatively with Tl and PCB 180 (PIPs > 0.8, except for $PIP_{BMA} = 0.75$ for Tl). LEPT was also found to be negatively associated with PCB 180 (PIPs > 0.8). In addition, BKMR

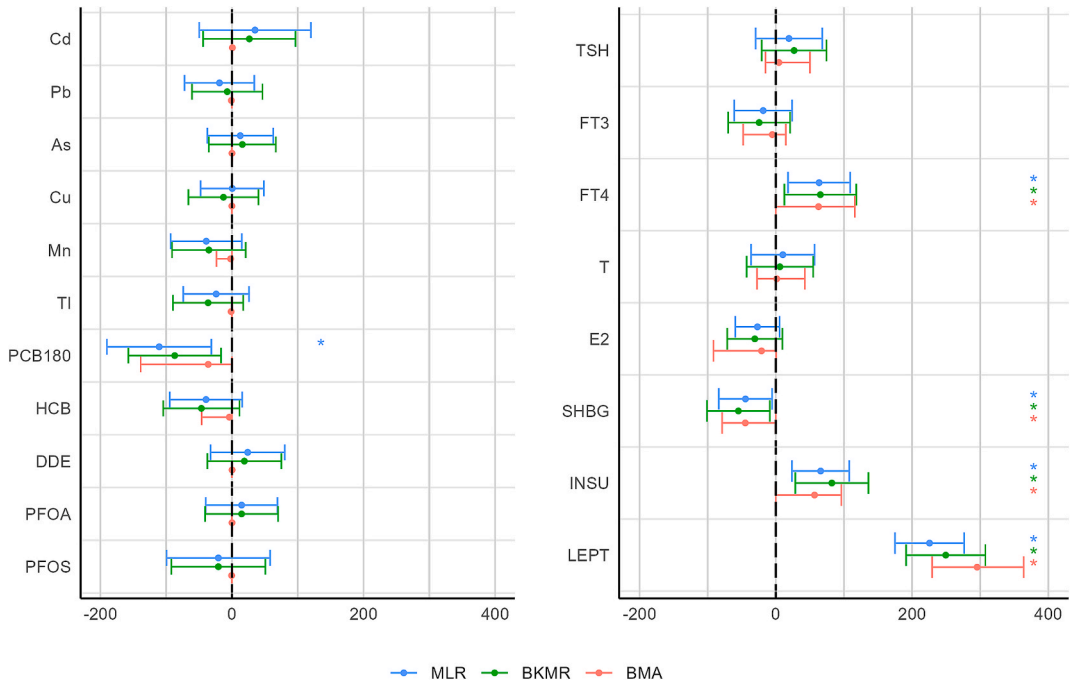

Fig. 1. Associations between exposure biomarkers in cord blood and birth weight (left panel) and between hormones in cord blood and birth weight (right panel) of newborns from the Flemish Environment and Health Studies, Flanders (FLEHS II & III, n = 432), estimated by three statistical methods for handling the mixture of exposures (left panel) or the mixture of hormones (right panel): multiple linear regression (MLR), Bayesian kernel machine regression (BKMR), and Bayesian model averaging (BMA). Estimates (with 95 % CI for MLR and 95 % CrI for BKMR and BMA) represent the change in mean birth weight (g) for an IQFc in exposure biomarker or hormone concentration, adjusted for other exposure biomarkers or hormones, gestational age (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy, cord blood cholesterol, and study cycle. Relevant associations are indicated with a star: exposures with a *P*-value < 0.05 in MLR, and exposures with a PIP > 0.7 in BKMR and BMA. Abbreviations: FLEHS, Flemish Environment and Health Study; Pb, lead; As, total arsenic, Cu, copper; Mn, manganese, Tl, thallium; PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; DDE, dichlorodiphenyldichloroethylene; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T, testosterone; ESTR, estradiol; SHBG, sex hormone-binding globulin; INSU, insulin; LEPT, leptin; CI, confidence interval; CrI, credible interval; IQFc, interquartile fold change; PIP, marginal posterior inclusion probability.

results provided some evidence for a positive association between As and INSU (PIP = 0.71) that appeared to be somewhat stronger at lower concentrations of PCB 180 (Supplementary Fig. S6), which might explain why this association was not picked up by MLR (P = 0.19) and BMA (PIP = 0.26). BKMR plots also showed some trends for steeper slopes at higher exposure concentrations in Cu-E2, Cu-SHBG, and PCB-LEPT associations (Supplementary Fig. S6). However, the evidence for interaction effects and nonlinearity was not very strong, so BMA results were considered as main output. Estimated geometric mean ratios for an IQFc in PCB 180 were 1.12 (95 % CrI: 1.00; 1.20) for SHBG, 0.86 (0.77; 1.00) for INSU, and 0.83 (0.73; 1.00) for LEPT.

Based on results from the exposure – hormone models, mediator models in mediation analyses were adjusted for Cd, Pb, As, Cu, Tl, and PFOA (in addition to the other covariates). Both single- and multiple-mediator (HDMA) models showed that the association between PCB 180 and birth weight was significantly mediated by FT4, SHBG, INSU, and LEPT concentrations (Table 3). Indirect effects (per IQFc in PCB 180) estimated by single-mediator and HDMA models were respectively −16 and −15 g for FT4, −14 and −12 g for SHBG, −23 and −15 g for INSU, and −53 and −51 g for LEPT. The overall indirect effect estimated by HDMA was −93 g, indicating that the four hormones mediated 94 % of the total effect of PCB 180 on birth weight.

Results from the sensitivity analysis excluding maternal diabetes cases (n = 8) were very similar (not shown). In another sensitivity analysis, cholesterol was not included as a covariate. Results from exposure – birth weight, hormones – birth weight, and exposure – hormone models (not shown) were similar to those from the main analysis, except that the evidence for the association between T and Tl was somewhat less strong (PIP_{BKMR} = 0.61 and PIP_{BMA} = 0.57 compared to PIP_{BKMR} = 0.79 and PIP_{BMA} = 0.75 in the main analysis), whereas the evidence for the association between T and PFAS was somewhat stronger (PIP_{BKMR} = 0.72 and PIP_{BMA} = 0.80 compared to PIP_{BKMR} = 0.66 and PIP_{BMA} = 0.64 in the main analysis). Also results of the single-mediator models were similar to those from the main analysis, showing significant mediation by FT4, SHBG, INSU, and LEPT (Supplementary Table S5). SHBG, however, was not picked up as important mediator by the multiple-mediator model, resulting in a lower estimate of the overall indirect effect (−77 g or 79 %). Results from the sensitivity analysis running stratified analyses by study (FLEHS II and FLEHS III), showed that the pooled result appeared to be driven by FLEHS III. Only for leptin consistent results were found in FLEHS II as well (Supplementary Fig. S7 and S8, Supplementary Table S6).

4. Discussion

In this study, we assessed the mediating role of thyroid, reproductive, and metabolic hormones in the association between chemical exposures and birth weight in healthy newborns from two successive birth cohorts of the FLEHS study (FLEHS II and III). A negative association was found between PCB 180 and birth weight. Consistently across methods, PCB 180 was positively associated with cord blood SHBG, and negatively associated with leptin and insulin. Similarly, thallium was positively associated with testosterone, estradiol, and SHBG, and negatively with insulin. Lead was positively associated with insulin. Different methods showed that higher FT4, insulin, and leptin were associated with higher birth weight, whereas higher SHBG was associated with lower birth weight. Mediation analysis for PCB 180 indicated that 94 % of the effect of this exposure on birth weight is mediated by FT4, SHBG,

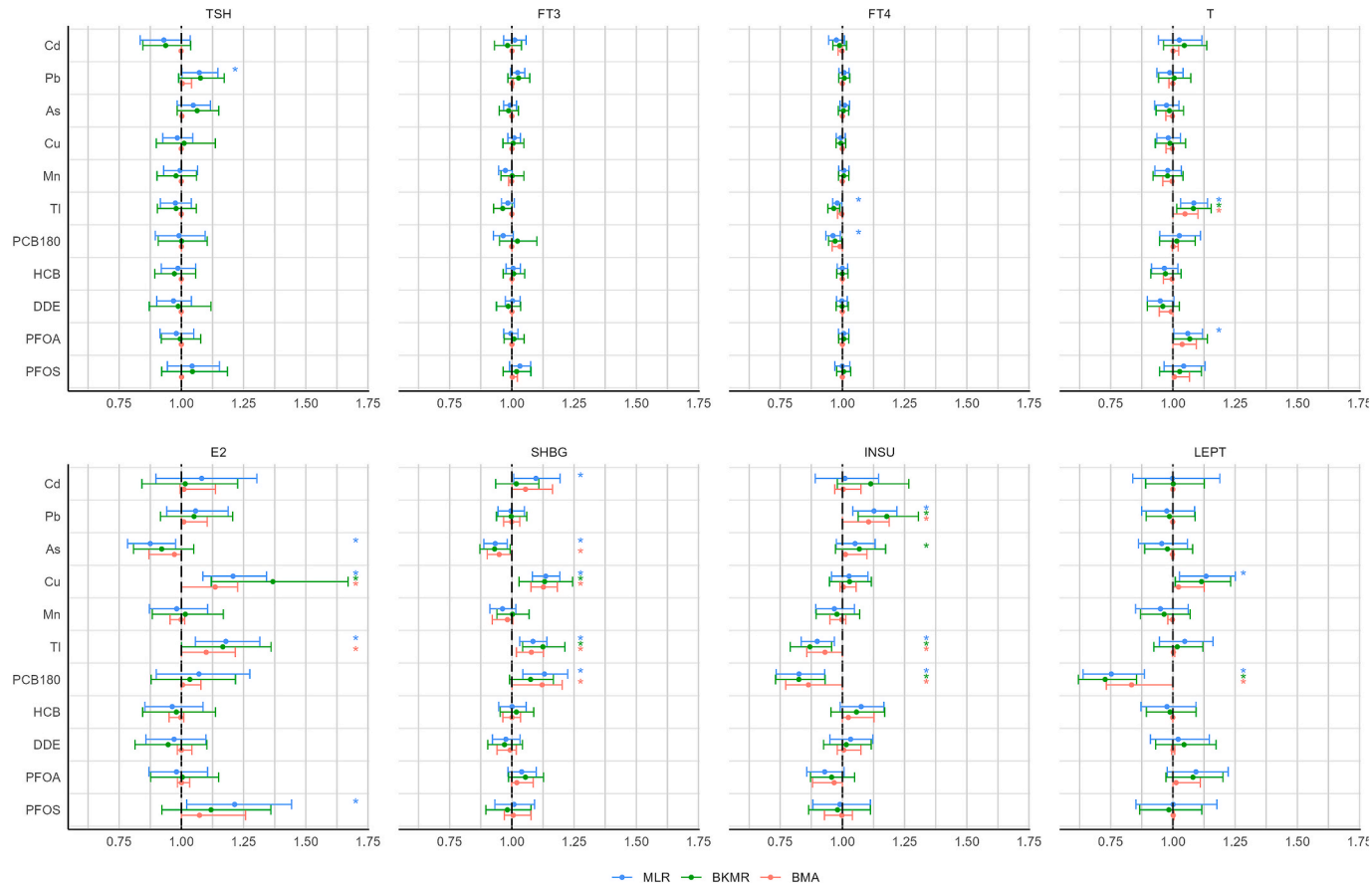

Fig. 2. Associations between exposure biomarker and hormone concentrations measured in cord blood of newborns from the Flemish Environment and Health Studies, Flanders (FLEHS II & III, n = 432), estimated by three statistical methods for handling the mixture of exposures: multiple linear regression (MLR), Bayesian kernel machine regression (BKMR), and Bayesian model averaging (BMA). Estimates (with 95 % CI for MLR and 95 % CrI for BKMR and BMA) represent the geometric mean ratio of hormone concentrations for an IQFc in exposure biomarker concentration, adjusted for other exposure biomarkers, gestational age (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy, cord blood cholesterol, and study cycle. Relevant associations are indicated with a star: exposures with a *P*-value < 0.05 in MLR, and exposures with a PIP > 0.7 in BKMR and BMA. Abbreviations: FLEHS, Flemish Environment and Health Study; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T, testosterone; ESTR, estradiol; SHBG, sex hormone-binding globulin; INSU, insulin; LEPT, leptin; Pb, lead; As, total arsenic, Cu, copper; Mn, manganese, Tl, thallium; PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; DDE, dichlorodiphenyldichloroethylene; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; CI, confidence interval; CrI, credible interval; IQFc, interquartile fold change; PIP, marginal posterior inclusion probability.

leptin, and insulin, with leptin contributing to more than half of this mediation effect. To our knowledge, this is the first epidemiologic study trying to unravel biological pathways linking chemical exposure and birth weight by assessing the combined effect of multiple hormones.

4.1. Association between chemical exposure and hormones

Although an association was found with birth weight only for PCB 180, more pollutants affected the hormone levels tested. These early changes may have consequences on health in later life and are risk factors for adverse development and metabolic health.

An inverse association was observed between PCB 180 with leptin and insulin. This decreasing trend was also observed for thallium and insulin, while lead on the other hand showed a positive association with insulin. It has been shown that obesogenic EDCs can alter the epigenome of multipotent stromal cells, which is preprogrammed toward an adipogenic fate (Janesick & Blumberg, 2011, 2012). A Slovakian birth cohort found an inverse association between PCB exposure and leptin levels within 7-year-old children (Palkovicova et al., 2013). In a clinical case-control study for nonalcoholic fatty liver disease, considered as the hepatic manifestation of metabolic syndrome, thallium was inversely associated with insulin levels (Asprouli et al., 2019). An article that reviewed the human, animal and in vitro studies that have examined the effects of lead exposure on the development of diabetes and related metabolic conditions, suggested a deleterious effect of environmental lead exposure on metabolic health (Leff et al., 2018). These findings support the hypothesis that exposures to endocrine disruptors interfere with metabolic pathways.

For the reproductive hormones studied, thallium was associated with increasing testosterone and estradiol levels. This positive trend was also observed for PCB 180 with SHBG. Halogenated chemicals interact with thyroid hormone- and sex-steroid-dependent systems which regulate early development (Mughal et al., 2018; Parent et al., 2011). PCB congeners act mainly as estrogens, while also anti-estrogenic, androgenic and anti-androgenic activities are described depending on the metabolite and the concentration (Flor et al., 2016). An in vivo study in rats indicated that the male reproductive system is a susceptible target site to the toxic effects of thallium (Formigli et al., 1986). They also suggest a major involvement of Sertoli cells in the mechanism underlying thallium-induced testicular damage.

Our study found no significant associations between the measured exposure biomarkers and the thyroid hormones. Several studies in rats demonstrated though the thyroid-disrupting effect of the pesticides DDT (Scollon et al., 2004) and HCB (Alvarez et al., 2005; van Raaij et al., 1993a; van Raaij et al., 1993b), as they decreased serum levels of thyroid hormones. Moreover, DDT and its metabolites, such as DDE, have been

Table 3
Mediating effect of cord blood hormones on the association between cord blood PCB 180 and birth weight of newborns from the Flemish Environment and Health Studies, Flanders (FLEHS II & III, n = 432), estimated by single-mediator and multiple-mediator (HDMA) models.

	Single-mediator models		HDMA	
	Estimate (95 % CI)	*P*-value	Estimate	*P*-value
Hormone-specific indirect effects				
TSH	−1 (−7; 5)	0.752		
FT3	−1 (−9; 5)	0.788		
FT4	−16 (−33; −3)	0.010	−15	0.007
T	−1 (−6; 4)	0.878		
ESTR	−4 (−14; 4)	0.430		
SHBG	−14 (−30; −2)	0.016	−12	0.023
INSU	−23 (−43; −6)	0.002	−15	0.003
LEPT	−53 (−87; −19)	0.006	−51	<0.001
Global indirect effect			−93	
Direct effect			−6	
Total effect			−99	
Percentage mediated			94 %	

Estimates represent the change in mean birth weight (g) for an IQFc in cord blood PCB 180. Outcome and mediator models were adjusted for gestational age (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy, cord blood cholesterol, and study cycle. Mediator models were additionally adjusted for Cd, Pb, As, Cu, Tl, and PFOA.
Abbreviations: PCB, polychlorinated biphenyl; FLEHS, Flemish Environment and Health Study; HDMA, High-dimensional mediation analysis; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T, testosterone; ESTR, estradiol; SHBG, sex hormone-binding globulin; INSU, insulin; LEPT, leptin; IQFc, interquartile fold change; Pb, lead; As, total arsenic; Cu, copper; Tl, thallium; PFOA, perfluorooctanoic acid.

confirmed as thyroid-disrupting chemicals in a Dutch prospective cohort study (de Cock et al., 2014). The median exposure level of DDE (82 ng/g lipid) in this cohort was higher than in our study (74 and 55 ng/g lipid in FLEHS II and III respectively). In addition, PCBs and PFAS bind to thyroid transport proteins, such as transthyretin, displace thyroxine, and disrupt thyroid function (Duntas & Stathatos, 2015; Gundacker et al., 2022). Another epidemiological study has described mainly negative associations between PCB congeners and maternal and fetal thyroid hormones (Maervoet et al., 2007). Samples in this study were obtained between 2002 and 2004 and consequently the observed PCB levels were higher in comparison with our study.

4.2. Association between chemical exposure and birth weight

A previous study of our research group pooling data from the 3xG study, FLEHS I, FLEHS II, and FLEHS III, resulting in a higher sample size, showed that PCB 180 was associated with a lower birth weight, while DDE was associated with higher birth weight (Govarts et al., 2020). The finding for DDE could however not be replicated in the current study, probably due to lower power. Also, the evidence for the association with PCB 180 was weaker, but still pointing towards an inverse association with birth weight. Nowadays, many studies perform mixture exposure-effect analyses with the sum of PCBs. PCB mixtures present in different study populations may differ, as relative toxicities between the different PCBs. It was decided to only include PCB 180 in our analyses, as this PCB congener was found to be most consistently associated with birth weight in our previous study, and to avoid multicollinearity by including the other PCBs measured. Moreover, it is one of the indicators and more abundant PCBs in human plasma or serum (Ferrante et al., 2014). However, the estimated effects attributed now to PCB 180 may also reflect other correlated PCB congeners.

Regarding prenatal exposure to PCB 180 and remaining congeners, studies have reported inconsistent findings when investigating birth weight. Some reported inverse associations with this outcome (Govarts et al., 2020; Karmaus & Zhu, 2004; Murphy et al., 2010; Patel et al., 2018) which are in line with our observations, while others reported inconclusive results (Grandjean et al., 2001; Longnecker et al., 2005; Mendez et al., 2010). Possible reasons for these differences might be lower samples size (less power), different range of exposure levels, time frame of the studies, etc. A *meta*-analysis revealed a negative correlation between PCBs exposure (including PCB 180) and birth weight (Zou et al., 2019).

4.3. Mediation by hormones and modes of action (MoA)

There are plausible pathways through which PCBs may alter birth weight, and consequently the future health of newborns, since they can cross the placenta and therefore interact directly with the fetus' organs (Wang et al., 2021). In this study, single- and multiple-mediator analyses showed that leptin, insulin, FT4, and SHBG could mediate the inverse association between PCB 180 and birth weight. Thus, our findings suggest that PCB 180 may disrupt the developmental hypothalamic–pituitary–thyroid axis, which may impair the adipokine axis, fat metabolism, and general development (Chou & Henderson, 2014).

Recent studies highlighted the role of fetal thyroid function, particularly FT4, for fetal growth and development (Medici et al., 2013; Shields et al., 2011a), and in another study, FT4 played a mediation role between particle air pollution and lower birth weight (Janssen et al., 2017). These trends are particularly concerning, since early hypo- or hyperthyroidism or thyroid receptor alterations can cause permanent behavioral, intellectual, and neurologic dysfunction (Fan et al., 2021).

Adiponectin, insulin, and leptin are key hormones that regulate fat mass storage and energy homeostasis and could, therefore, support the plausibility of these growth-related hormones as mediators of PCB 180-lower birth weight association (Stern et al., 2016). This mechanism may be mediated by the thyroid axis and required for the development of fat metabolism (Ferrante et al., 2014; Shields et al., 2011; Stern et al., 2016). In this regard, it is known that PCBs can accumulate in fat tissue and promote adipogenesis by activating C/EBPβ (Yu et al., 2021). Another *in vitro* study showed that non-dioxin like PCBs altered lipid content and metabolism in 3T3-L1 adipocytes, moreover impairment of leptin signaling was induced (Ferrante et al., 2014). Our study observed that insulin and leptin are positively associated with birth weight. Leptin is considered as one of the markers associated with fetal growth restriction (FGR) (Sun, 2022) and plays a role in the development and maturation of organs, including the heart, brain, kidneys and pancreas (Briffa et al., 2015). In those studies reporting an association between leptin and FGR, a positive association was found between leptin and birth weight (Pighetti et al., 2003; Stefaniak & Dmoch-Gajzlerska, 2022), in line with our findings. Alterations in plasma leptin during development may be associated with an increased risk of developing a number of adulthood diseases, including cardiovascular, metabolic, and renal diseases via altered fetal development and organogenesis (Briffa et al., 2015).

Regarding the mediation role of SHBG, PCB congeners (assessed as PCB congener mixture) can displace reproductive hormones by binding to circulating SHBG and intracellular hormone receptor binding sites (Troisi et al., 2020), which would impact the bioavailability of reproductive hormones, thus affecting embryo development.

The use of effect biomarkers (in this case hormones) in human biomonitoring studies provides an additional value allowing to explore biological pathways in exposure-effect analyses, and as such can strengthen causal interpretation of exposure-effect associations in epidemiologic studies. Reliable effect biomarkers are available for most of the relevant MoAs (Zare Jeddi et al., 2021). Moreover, effect biomarkers have in many cases reached a level of maturity ensuring use in chemical mixture risk assessment (Ladeira, 2024; Zare Jeddi et al., 2021).

5. Strengths and limitations

This study has several limitations that should be noted for transparency and accurate interpretation of the results. Firstly, unmeasured confounding factors, including other exposures and covariates, are possible. To avoid multicollinearity, we selected PCB 180 to represent all correlated PCBs in the statistical analyses, so estimated effects for PCB 180 might be (partly) attributed to one or more other PCB congeners or other exposures not included in the model. Notably, caution should be taken due to the cross-sectional nature of this study, i.e., prenatal exposure and hormone levels were obtained simultaneously using cord blood samples, which were taken immediately after delivery, when birth weight was also measured. As POPs are persistent, it could however be assumed that they reflect prenatal exposure. However, some hormones could be considered markers for low birth weight, indicating we cannot exclude reverse causality when assessing the mediation effect, that is producing an artificial mediation effect of hormones between exposure and birth weight. Especially for the metabolic markers, associations were reported between low birth weight and elevated levels of insulin and leptin (Jornayvaz et al., 2016; Obeng et al., 2024; Verhaeghe et al., 2006). Therefore, one should be cautious with the interpretation of the results of the mediation analysis. However, the results found for the association between some of the exposure markers and the hormones demonstrated the endocrine disrupting effect of these chemicals. Moreover, smoking during pregnancy was self-reported via questionnaires, which could lead to under-reporting.

One of the study's strengths was the pooling of two birth cohorts from Flanders that can be considered as relatively homogeneous study populations. Consistent sampling protocols and the use of the same laboratories for the exposure biomarkers also added to the study's robustness. This was not true for the hormones which were analyzed in two different laboratories by different methods. Therefore, it was decided to additionally center the hormone variables per study cycle and moreover adding study cycle as fixed covariate to the models. Moreover, rather than concentrating on the impact of a single exposure, this study investigated the influence of a mixture of chemicals by incorporating multiple exposure biomarkers into the same model, thereby accounting for confounding by other chemicals. We used different statistical methods for this purpose, confirming the robustness of our findings. Similarly, multi-dimensional effect biomarker data on hormone concentrations were integrated, and correlations between hormones were adjusted by treating them as a "mixture" when assessing their effect on birth weight. Finally, the multiple-mediator approach used for studying their role in the association between chemical exposure and birth weight reduced the risk of bias. It enabled the assessment of combined mediation effects and the relative importance of the various hormones.

6. Conclusion

This study provides novel insights into the biological mechanism underlying the adverse health effects of prenatal multipollutant exposure. Characterization of the mechanisms targeted by environmental exposures may add to the weight of evidence in the observed associations between exposure and effect in epidemiological studies. Further research is needed to refine strategies for evaluating the health risks of real-life exposure to mixtures. To achieve this, advancing the statistical methods for multi-exposure and multi-mediator modeling is a domain for which further development is crucial. The results of this thesis emphasize the importance of early life exposures and suggest that current exposure levels in the Flemish population may be associated with adverse health outcomes. These research findings improve chemical risk assessment and add to the weight of evidence linking exposure to endocrine disruptors with adverse birth outcomes.

CRediT authorship contribution statement

Eva Govarts: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bianca Cox:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Lützen Portengen:** Writing – review & editing, Supervision, Methodology. **Andrea Rodríguez-Carrillo:** Writing – review & editing, Writing – original draft, Visualization. **Madeline Carsique:** Writing – review & editing. **Adrian Covaci:** Writing – review & editing. **Elly Den Hond:** Writing – review & editing. **Stefaan De Henauw:** Writing – review & editing. **Tim Nawrot:** Writing – review & editing. **Martine Leermakers:** Writing – review & editing, Resources. **Lisbeth Patteet:** Writing – review & editing, Resources. **Thomas Schettgen:** Writing – review & editing, Resources. **Amélie Crépet:** Writing – review & editing. **Jacob Van Klaveren:** Writing – review & editing. **Roel Vermeulen:** Writing – review & editing, Supervision, Conceptualization. **Greet Schoeters:** Writing – review & editing, Supervision, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109700.

Data availability

The authors do not have permission to share data.

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