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Early-life exposure to multiple persistent organic pollutants and metals and birth weight: Pooled analysis in four Flemish birth cohorts

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ABSTRACT

Background and aims: Prenatal chemical exposure has frequently been associated with reduced fetal growth although results have been inconsistent. Most studies associate single pollutant exposure to this health outcome, even though this does not reflect real life situations as humans are exposed to many pollutants during their life time. The objective of this study is to investigate the association between prenatal exposure to a mixture of persistent environmental chemicals and birth weight using multipollutant models.

Methods: We combined exposure biomarker data measured in cord blood samples of 1579 women from four Flemish birth cohorts collected over a 10 years' time period. The common set of available and detectable exposure measures in these cohorts are three polychlorinated biphenyls (PCB) congeners (138, 153 and 180), hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (*p,p'*-DDE) and the metals cadmium and lead. Multiple linear regression (MLR), Bayesian Information Criterion (BIC), penalized regression using minimax concave penalty (MCP) and Bayesian Adaptive Sampling (BAS) were applied to assess the influence of multiple pollutants in a single analysis on birth weight, adjusted for *a priori* selected covariates.

Results: In the pooled dataset, a median (P25-P75) birth weight and gestational age of 3420 (3140–3700) grams and 39 (39–40) weeks was observed respectively. The median contaminant levels in cord blood were: 15.8, 26.5, 18.0, 16.9 and 91.5 ng/g lipid for PCB 138, PCB 153, PCB 180, HCB and *p,p'*-DDE, respectively, 0.075 μg/L for cadmium and 9.7 μg/L for lead. According to the applied statistical methods for multipollutant assessment, *p,p'*-DDE and PCB 180 were most consistently associated with birth weight. In addition, PCB 153 was selected when applying MCP and BAS. An inverse association with birth weight was found for the PCB congeners, while an increased birth weight was observed for elevated levels of *p,p'*-DDE.

Conclusions: Assessing the health risk of combinations of exposure biomarkers reflects better real-world situations and thereby allows more effective risk assessment. Our results add to the existing evidence based on detrimental effects of PCBs on birth weight and indicate a possible increase in birth weight due to *p,p'*-DDE (while correcting for PCBs).

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1. Introduction

A suboptimal intra-uterine environment can affect fetal growth and contribute to the risk of developing adult disease (Barker 1998). Humans, as such also pregnant women, are exposed to many chemicals during their lifetime via diet, inhalation, non-dietary ingestion and dermal absorption. Many of these chemical compounds are, due to their high lipophilicity or amphoteric properties, transported via the placenta to the fetus (Vizcaino et al., 2014). Prenatal chemical exposure has frequently been associated with reduced fetal growth although results have been inconsistent (see further). Human biomonitoring shows that complex mixtures of xenobiotic chemicals are present in the prenatal environment (Martínez et al., 2020; Rovira et al., 2019; UBA, 2014). In three successive human biomonitoring campaigns among newborns of the Flemish Environment and Health Studies (FLEHS I, II & III) and another regional birth cohort (3xG), we measured a diverse set of biomarkers in human samples, i.e. cord blood and blood, hair and urine of the mother. The common set of available and detectable exposure measures in these cohorts were three polychlorinated biphenyl (PCB) congeners (138, 153 and 180), hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (*p,p'*-DDE) and the metals cadmium (Cd) and lead (Pb) measured in cord blood.

To date, most epidemiological studies have investigated associations between single pollutant exposures and birth weight or other fetal growth measures like birth length, head circumference, small for gestational age, etc., and most of them reported significant inverse associations for the selected compounds, e.g. lower fetal growth for increased concentrations of HCB (Eggesbo et al., 2009), PCBs (Casas et al., 2015; Govarts et al., 2012) and Cd (Guo et al., 2017; Kippler et al., 2012). However, results are inconsistent with several studies observing no significant associations (Berkowitz et al., 1996; Gladen et al., 2003; Khanjani and Sim, 2006; Longnecker et al., 2005; Wolff et al., 2007). Investigating associations of single pollutant exposures to health outcomes does not reflect real life situations whereas humans are exposed to thousands of pollutants during their life time (Cohen and Jefferies, 2019). Several biomonitoring studies have looked at the association of multiple exposures with fetal growth, focusing on different chemical exposures, e.g. phthalates (Chiu et al., 2018; Philippat et al., 2019), organochlorine compounds (Govarts et al., 2018; Vafeiadi et al., 2014), pesticides (Béranger et al., 2020) or multiple chemical classes (Govarts et al., 2016; Kalloo et al., 2020; Lee et al., 2020; Lenters et al., 2015; Woods et al., 2017). These studies used different statistical methods to analyse the multiple exposures in association with fetal growth, e.g. ordinary regression models (Chiu et al., 2018; Govarts et al., 2018; Vafeiadi et al., 2014), Principal Component Regression (PCR) or another clustering technique (Chiu et al., 2018; Govarts et al., 2016; Kalloo et al., 2020; Lee et al., 2020), Structural Equation Models (SEM) (Chiu et al., 2018), exposure summation or z-scores (Cabrera-Rodriguez et al., 2018; Govarts et al., 2016), elastic net (ENET) (Béranger et al., 2020; Lenters et al., 2015) and/or Bayesian techniques (Chiu et al., 2018; Woods et al., 2017).

The field of statistical tools to explore the association of multiple chemical exposures on health outcomes has evolved in recent years. Several methods have been developed, which can be classified into three groups: dimension reduction (e.g. PCR, partial least square regression (PLS)), variable selection (e.g. deletion/substitution/addition algorithm, penalized methods like ENET, and Bayesian variable selection methods) and grouping of observations (e.g. cluster analysis, building groups based on an exposure score, Bayesian profile regression, recursive partitioning techniques) (Stafoggia et al., 2017). Several simulation studies (Agier et al., 2016; Bobb et al., 2015; Lenters et al., 2018; Sun et al., 2013) have been performed to explore the performance of these techniques. These simulations have not identified a universal best performing method, but have demonstrated clearly that classic single-variable or multivariable models do not suffice under most circumstances.

The objective of this study is to investigate the association between prenatal exposure to a mixture of environmental chemicals and birth weight in the pooled dataset of four Flemish birth cohorts by comparing results obtained from different statistical models. Combining these cohorts also provides the opportunity to study possible associations of birth weight with a correlated group of exposures in a homogeneous population collected by subsequent sampling over a 10 years' time period.

2. Methods

2.1. Description of cohorts

We pooled data from three successive newborn campaigns of the Flemish Environment and Health Studies (FLEHS I, II and III) and a regional birth cohort (3xG). Details of the recruitment protocols have been reported for the FLEHS studies (Baeyens et al., 2014; De Craemer et al., 2016; Den Hond et al., 2009). In FLEHS I, participants were recruited between 2002 and 2004 in eight geographical areas covering 22% of the surface area of Flanders and 20% of the population. Two areas were urban locations (Antwerp city and Ghent city), four areas were characterized by industrial settings (Ghent and Antwerp harbor, non-ferrous industry, chemical industry and areas around waste incinerators), one area had intensive fruit cultivation (fruit growing area), and one area was less densely populated and had no registered emissions (rural area). In FLEHS II and III participants were recruited from the general population of the five Flemish provinces between 2008 and 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 with the number of inhabitants in that province. The 3xG mothers were recruited from three bordering rural communities (Dessel, Mol and Retie). All mothers that fulfilled the inclusion criteria and gave birth between 2010 and 2015 were invited to participate. In total 1196, 255, 281 and 301 mother-newborn pairs were obtained from FLEHS I, II, III, and 3xG respectively. All participants signed an informed consent. Inclusion criteria were to be able to fill out a Dutch questionnaire and to live at least five years in the selected study areas (FLEHS I), at least 10 years in Flanders (FLEHS II), at least five years in Flanders (FLEHS III), or living in the recruitment area (3xG). The biomonitoring studies were approved by the Ethical Committee of the University of Antwerp and the University Hospital of Antwerp (all studies) and additionally by the Ethical Committees of the local hospitals if relevant.

The study population was restricted to live-born singleton births, with available measurements of the selected exposure markers, outcome and the *a priori* selected covariates. The outcome of interest was birth weight, which 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: maternal age at delivery ($<$27, 27 $<$ 30, 30 $<$ 33, $\geq$33 years), maternal pre-pregnancy body mass index (BMI; $<$18.5, 18.5 $<$ 25, 25 $<$ 30, $\geq$30 kg/m^2), parity (0, 1, $\geq$2) and maternal smoking during pregnancy (non-smoking, smoking). Cohort was included as an additional covariate. In total, we used the data from 1579 mother-newborn pairs.

2.2. Exposure assessment

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. After completion of the recruitment period, all the samples, together with field work blanks and control samples, were transported in batch from the central lab to the different analytical laboratories. The

common group of exposure biomarkers measured in cord blood in the four birth cohorts consisted of specific PCB congeners (PCB 138, PCB 153, PCB 170 and PCB 180), *p,p'*-DDE, the major metabolite of DDT, the organochlorine pesticide HCB, and the metals lead and cadmium. PCB 170 measurements had more than 50% of the samples below the limit of quantification (LOQ) for FLEHS I and FLEHS II. We therefore excluded PCB 170 from further analyses leaving a total of 7 selected exposure biomarkers.

The persistent organic pollutants (POPs) were measured in cord plasma by gas chromatography-electron capture negative ionization mass spectrometry (Covaci and Voorspoels, 2005). In FLEHS I, the plasma total lipid concentration was determined gravimetrically. In case no value could be obtained gravimetrically, total lipid concentration was calculated based on routinely measured triglycerides and total cholesterol by the formula deducted from the samples for which lipid measures was available: total lipids = 50.49 + 1.32 × (cholesterol + triglycerides) in mg/dL. For FLEHS II, III and 3xG 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. The analysis of all chlorinated compounds was performed by the same laboratory of the University of Antwerp by the same analytical method, however the method was improved over time leading to lower LOQs in FLEHS III and 3xG. The LOQ for all chlorinated compounds in plasma was 20 ng/L in FLEHS I and II, and for *p,p'*-DDE in all campaigns. The LOQ for the PCB congeners was 2 ng/L and 10 ng/L for FLEHS III and 3xG respectively, and for HCB the LOQ was 10 ng/L in the FLEHS III and 3xG campaigns.

Metals were measured in whole cord blood by high resolution inductively coupled plasma-mass spectrometry (Schroijen et al., 2008). The measurements of Cd and Pb were performed by the same laboratory of the Free University of Brussels by the same analytical method, however the method was improved leading to lower LODs in FLEHS III and 3xG. The limits of detection (LODs) ranged from 0.0097 to 0.09 μg/L for cadmium and from 0.04 to 2 μg/L for lead.

Data below the LOD or LOQ (1.1–27% depending on the compound) were single imputed from a log-normal probability distribution, where the mean was allowed to depend on the study population and observed values for the other contaminants and the residual variance to vary by population (Lubin et al., 2004).

2.3. Statistical analysis

Exposure variables were ln-transformed to reduce the influence of outliers. We assessed correlations between (ln-transformed) exposures using Pearson's correlation coefficients. For the models, we mean-centered and standardized all predictor variables. To estimate the association between the multiple pollutants and birth weight, we used five linear regression-based statistical methods, i.e. multiple linear regression (MLR), model selection and Bayesian model averaging using the Bayesian Information Criterion (BIC) (Schwarz, 1978), penalized regression (Zou and Hastie, 2005), and Bayesian Adaptive Sampling (BAS) (Liang et al., 2008). The models included all *a priori* selected covariates, without subjecting them to variable selection. Estimated slope coefficients are presented as the expected change in mean birth weight (grams) per interquartile fold change in exposure (IQFc; the fold change of the 75th percentile over the 25th percentile in exposure), of cord plasma/blood exposure levels.

The assumption of linearity was assessed by fitting single pollutant models using general additive models (GAMs) to evaluate the shape of the associations between the exposures and outcome. Possible effect modification was investigated by adding interaction terms between single exposures and each of the covariates and between pairs of exposures.

2.3.1. Multiple linear regression (MLR)

Ordinary linear regression was applied as most conventional model to estimate exposure-effect associations, by including all exposure biomarkers in a single multiple linear regression model. Statistical significance of the association between the exposure markers and birth weight was assessed by the *p*-value. We assessed collinearity by estimating variance inflation factors (VIFs), with VIF greater than 5 suggesting a problem of collinearity (Kleinbaum et al., 2013).

2.3.2. Bayesian Information Criterion (BIC)

Model selection among a finite set of models can be performed by comparing BICs, but only when the number of candidate predictors/exposures is not too high, because it requires evaluation of model fit for all (competing/different) regression models (Claeskens, 2016). With 7 different exposure biomarkers, there are only 128 different models (2^p where p is the number of exposure biomarkers) that need to be evaluated, which makes the approach feasible in this study. Statistical inference based on estimated regression coefficients and 95% confidence intervals from the selected "best" or "median probability" models is flawed, because it does not take into account the selection process. With only a limited number of potential models to choose from, it is possible to estimate 95% confidence intervals that have guaranteed coverage probability under arbitrary model selection using the approach suggested by Berk et al., (Berk et al., 2013), which is implemented in the R package PoSI.

Although BIC is often used to select only a single "best-fitting" model, it can also be used more comprehensively to evaluate model uncertainty by using BIC to approximate Bayesian posterior model probabilities. By summing the posterior probabilities of all models in which a biomarker occurs, it is possible to estimate the so-called marginal posterior probability of inclusion (MPPI) for each exposure biomarker. We can then either fit a model that includes only exposures with a MPPI exceeding a certain threshold (for instance 50%; the so-called median probability model (Barbieri and Berger, 2004)) or base our inference on the full range of models as in (Bayesian) model averaging. In Bayesian model averaging (BMA) (Hoeting et al., 1999), MPPIs are used as weights to estimate a full posterior distribution for each regression coefficient, which can be summarized using 95% (Bayesian) credible intervals (95% BCI). The R package BAS was used to implement the Bayesian model averaging approach using BIC and to estimate 95% credible intervals for all regression coefficients (Clyde, 2020).

2.3.3. Penalized regression using minimax concave penalty (MCP)

Penalized regression methods were developed to address the problems of multicollinearity and high dimensionality, which cause MLR to produce unreliable parameter estimates and prevent efficient model exploration (Chadeau-Hyam et al., 2013). In MLR, regression coefficients are estimated by minimizing the residual sum of squares (i.e. maximizing model fit), while in penalized regression models coefficients are estimated by jointly minimizing the residual sum of squares and a function of the estimated coefficients. For the well-known LASSO penalty that function is the absolute value of the coefficients, and it can be shown that this leads to effective variable selection because some of the coefficients are shrunken to exactly zero thereby effectively removing the variable from the model. We used a variant of LASSO that uses the minimax concave penalty (MCP), and is implemented in the R package ncvreg (Breheny and Huang, 2011). We used 10-fold cross-validation to determine the optimal degree of the penalization and stability selection to allow finite sample control of error rates by modifying routines from the R package stabsel (Shah and Samworth, 2013).

As for the approach using the "best" or "median probability" models based on BIC, we fitted the model using the selected exposures from stability selection and adjusted the reported 95% confidence intervals using the R package PoSI.

2.3.4. Bayesian Adaptive sampling (BAS)

BAS is a Bayesian model averaging technique that can use either sampling or enumeration to explore different model structures (Liang

et al., 2008). We used enumeration to explore all possible 128 different regression models and calculated the marginal variable inclusion probabilities (MPPI) for each exposure biomarker using the posterior sampling probabilities for each model in which they were included. Like for BIC-BMA, a threshold of 50% for the MPPIs could be used to select exposures or we could base our inference on the full range of models. We used the Jeffreys-Zellner-Siow prior (Zellner and Siow, 1980) for the regression coefficients and a uniform (flat) prior on the model space. The R-package BAS was used to implement the analyses and estimate point estimates and 95% Bayesian credible intervals (BCI) using the full posterior distribution of all regression coefficients.

All statistical analyses were performed in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

In the pooled data, a median (P25-P75) birth weight and gestational age of 3420 (3140–3700) grams and 39 (39–40) weeks was observed respectively. There was some variation across the different birth cohorts in birth weight (Table 1). Median maternal age and pre-pregnancy BMI at delivery were similar across cohorts, 30 years and 23 kg/m^2 respectively (Table 1). An increasing trend of pre-pregnancy BMI $\geq$ 30 kg/m^2 was however observed over time (from 7% in FLEHS I to 10% in FLEHS III). Half the mothers were nulliparous (42–59%). Still 14% of the mothers smoked during pregnancy, but over the study periods the percentage dropped from 16% (FLEHS I) to 12% (FLEHS II) to 11% (FLEHS III), with 3xG having the lowest percentage of smoking mothers (8%) (Table 1).

Table 1
Characteristics of the participants of the 4 birth cohorts.

Characteristics	FLEHS I (2002–2004)	FLEHS II (2008–2009)	FLEHS III (2013–2014)	3xG (2011–2015)
N[a]	957	224	273	125
Birth weight (g)	3395 (3120–3660)	3518 (3180–3778)	3420 (3155–3720)	3430 (3200–3730)
Gestational Age (weeks)	39 (39–40)	40 (39–40)	39 (39–40)	40 (39–40)
Child's sex				
Boy	496 (51.8%)	116 (51.8%)	139 (50.9%)	63 (50.4%)
Girl	461 (48.2%)	108 (48.2%)	134 (49.1%)	62 (49.6%)
Maternal age at delivery (years)	29.7 (26.7–32.2)	30.2 (27.5–32.7)	30.1 (27.3–33.2)	29.6 (27.5–31.6)
Maternal age at delivery				
< 27 years	254 (26.5%)	51 (22.8%)	61 (22.3%)	24 (19.2%)
27 < 30 years	249 (26.0%)	57 (25.5%)	74 (27.1%)	44 (35.2%)
30 < 33 years	265 (27.7%)	65 (29.0%)	68 (24.9%)	37 (29.6%)
≥ 33 years	189 (19.8%)	51 (22.8%)	70 (25.6%)	20 (16.0%)
Maternal pre-pregnancy BMI (kg/m^2)	22.5 (20.3–25.1)	22.5 (20.4–24.9)	23.1 (20.8–25.8)	22.8 (21.0–25.8)
Maternal pre-pregnancy BMI				
<18.5 kg/m^2	56 (5.9%)	14 (6.3%)	7 (2.6%)	5 (4.0%)
18.5 < 25 kg/m^2	654 (68.3%)	157 (70.1%)	181 (66.3%)	83 (66.4%)
25 < 30 kg/m^2	180 (18.8%)	34 (15.2%)	59 (21.6%)	23 (18.4%)
≥ 30 kg/m^2	67 (7.0%)	19 (8.5%)	26 (9.5%)	14 (11.2%)
Parity				
0	568 (59.4%)	93 (41.5%)	122 (44.7%)	65 (52.0%)
1	270 (28.2%)	71 (31.7%)	98 (35.9%)	47 (37.6%)
≥ 2	119 (12.4%)	60 (26.8%)	53 (19.4%)	13 (10.4%)
Maternal smoking during pregnancy				
Non-smoking	800 (83.6%)	197 (88.0%)	243 (89.0%)	115 (92.0%)
Smoking	157 (16.4%)	27 (12.1%)	30 (11.0%)	10 (8.0%)

Continuous measures described by median (P25-P75); categorical measures described by frequencies (%).
Abbreviations: BMI, body mass index; P, percentile.
[a] Number of live-born singleton births with exposure levels and information on birth weight and the selected covariates gestational age, sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, maternal smoking during pregnancy and cohort.

The median contaminant levels in cord blood were: 15.8 ng/g lipid for PCB 138, 26.5 ng/g lipid for PCB 153, 18.0 ng/g lipid for PCB 180, 16.9 ng/g lipid for HCB, 91.5 ng/g lipid for *p,p'*-DDE, 0.075 μg/L for Cd and 9.7 μg/L for Pb (Fig. 1, Supplemental Material, Table S1). For all compounds, a decline over time was observed across the three successive FLEHS campaigns (Fig. 1, Supplemental Material, Table S1). Correlations between the different pollutants were low to moderate (Pearson's $r = 0.12$–0.58), except for the three PCB congeners that were highly correlated (Pearson's $r = 0.75$–0.83) (Fig. 2).

In single pollutant models, increased levels of all PCB congeners were significantly associated with reduced birth weight (Fig. 3). The other exposure markers were not significantly associated with birth weight in the single pollutant models. Only PCB 180 and *p,p'*-DDE were significantly associated with birth weight in the MLR model (Fig. 3, Supplemental Material, Table S2). Some of the exposures were rather strongly correlated, causing inflation of the variance and as such larger CIs for the estimates (Supplemental Material, Table S2). However, VIFs were all < 5 indicating that the problem of collinearity was marginal in this large study population with few candidate exposures. Using BIC as the selection criterion, the model with PCB 180 and *p,p'*-DDE was selected as "best" model. This was confirmed in the BMA approach using BIC for which PCB 180 and *p,p'*-DDE were both being associated with birth weight, with a MPPI of 70% and 78% respectively (Fig. 3, Supplemental Material, Table S2). PCB 153, PCB 180 and *p,p'*-DDE were selected in MCP models after stability selection (Fig. 3, Supplemental Material, Table S2, Figure S1), with *p,p'*-DDE having the highest selection probability, followed by PCB 180 and PCB 153. These pollutants were also identified from the BAS model, with MPPIs of 51%, 84% and 95% for PCB 153, PCB 180 and *p,p'*-DDE respectively. Point estimates and 95% (B)CIs for each exposure based on model averaging are provided in the Supplemental Material (Table S2). PCB congeners PCB 153 and PCB 180 showed an inverse association with birth weight in all multipollutant models, while *p,p'*-DDE levels were associated with an increasing birth weight (Fig. 3, Supplemental Material, Table S2).

The linearity assumption was not rejected in single pollutant models and there was no evidence of effect modification as no significant interactions were found between exposures and covariates or pairs of exposures (data not shown).

4. Discussion

In this study, we examined the association between prenatal exposure to PCB 138, PCB 153, PCB 180, HCB, *p,p'*-DDE, cadmium and lead and birth weight in a pooled dataset of four Flemish birth cohorts. From all exposure measures, *p,p'*-DDE and PCB 180 were most consistently associated with birth weight according to five different multipollutant modeling approaches. In addition, PCB 153 was selected when applying MCP and BAS. An inverse association with birth weight was found for the PCB congeners, while an increased birth weight was observed for elevated levels of *p,p'*-DDE. No associations were found or retained for HCB, PCB congeners 170 and 138, and the metals Cd and Pb.

Five different approaches were used to assess the association between multiple exposures and birth weight. The results were comparable for this dataset with 7 exposures. Probably as proof of principle, these methods should also be explored in higher dimensional datasets with more exposures, where it has been shown that MLR does not work anymore (Agier et al., 2016). MLR also performs less in this study, as it was not able to pick-up PCB 153 due to variance inflation; and if a multiple comparison correction was applied also the association for PCB 180 was lost. The advantage of the MCP, BIC and BAS approaches is that

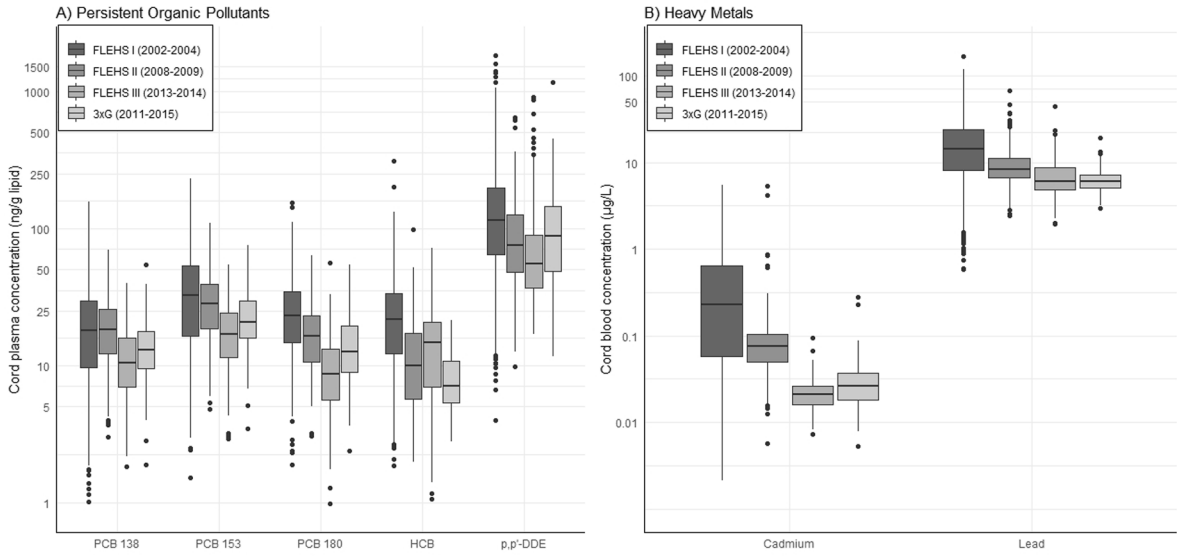

Fig. 1. Boxplots of distributions of exposure biomarker concentrations of A) PCB 138, PCB 153, PCB 180, HCB and *p,p'*-DDE in cord plasma (ng/g lipid), and B) Cd and Pb in cord whole blood (µg/L), per birth cohort. Horizontal lines correspond to medians, and boxes to the 25th-75th percentiles; whiskers extend to data within the interquartile range times 1.5, and data beyond this are plotted as dots. Abbreviations: PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; *p,p'*-DDE, dichlorodiphenyldichloroethylene; Cd, cadmium; Pb, lead.

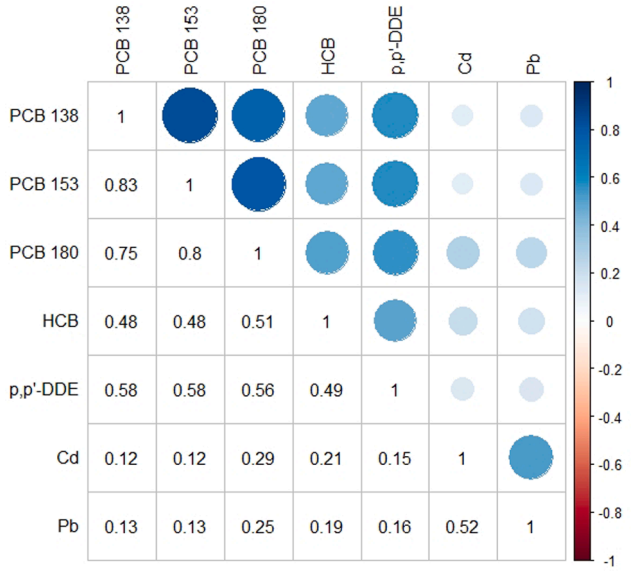

Fig. 2. Pearson correlation matrix between the ln-transformed exposure biomarkers. The color intensity of the circles indicates the strength of the correlation. Blue indicates a positive correlation, and red indicates a negative correlation. Abbreviations: PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; *p,p'*-DDE, dichlorodiphenyldichloroethylene; Cd, cadmium; Pb, lead. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

they provide a selection probability for each pollutant that can be used to estimate an error rate (either family-wise error rate of false discovery rate). MCP is a variable selection tool, whereas BAS tries to find the best subset model based on model averaging. The results of BAS can however be used for model selection and/or variable selection. In simulation studies (Agier et al., 2016; Bobb et al., 2015; Sun et al., 2013), it has been shown that no method outperforms all others across different datasets. The performances differ according to the nature of the outcome, the sample size, the number of pollutants, and the strength of the exposure–response association (Agier et al., 2016; Bobb et al., 2015; Sun et al., 2013). The choice of the method depends on the goal of the study: risk prediction, effect estimation or screening for important predictors and their interactions.

This study was set up as an explorative study to explore different statistical methods and to generate hypotheses. Based on the stability selection for MCP and MPPI for BIC-BMA and BAS, *p,p'*-DDE had the highest selection probability, followed by PCB 180 and PCB 153. The lower selection probability for the PCB congeners is likely at least partially due to the strong correlation between them. For the PCB congeners, an inverse association with birth weight was observed, while *p,p'*-DDE was associated with higher birth weight. The association between *p,p'*-DDE and birth weight could only be observed when assessed in models that included (at least) one of the PCB congeners, and not in the single pollutant models. This illustrates the fact that co-exposures should not be ignored when looking into exposure–response associations.

Our results show that *p,p'*-DDE and PCBs may have opposite effects on birth weight. The inverse association between PCB congeners and birth weight has been reported previously in several human studies assessing the association of single pollutants (Casas et al., 2015; Govarts et al., 2018; Lauritzen et al., 2017; Patel et al., 2018). In a pooled analysis of 9000 mother-newborn pairs obtained from 11 European birth cohorts, a significant inverse association was found between PCB 153 and birth weight (Casas et al., 2015), but no association was found for *p,p'*-DDE. Moreover, some studies have reported higher odds for small for gestational age with increasing levels of PCB 153 (Govarts et al., 2018; Lauritzen et al., 2017; Longnecker et al., 2005). However, results are inconsistent as some studies reported no or small associations of PCBs and birth weight (Cabrera-Rodriguez et al., 2018; Woods et al., 2017), or even opposite associations (Lignell et al., 2013). Till now, only two studies (Govarts et al., 2018; Vafeiadi et al., 2014) fitted a multi-pollutant regression model with several PCB congeners, *p,p'*-DDE and HCB, to assess the association between multiple exposure and birth weight. In Vafeiadi et al. (2014), the association with birth weight was mainly driven by HCB. In the pooled statistical analysis of Govarts et al. (2018) using multiple linear regression analysis, PCB 153 and HCB appeared to drive the association with SGA with no effect of *p,p'*-DDE, however in that study, there were no other PCB congeners included. In our study, PCB 180 was selected as stronger predictor of the three PCB congeners. Tang et al. (2018) reported that the association between PCB

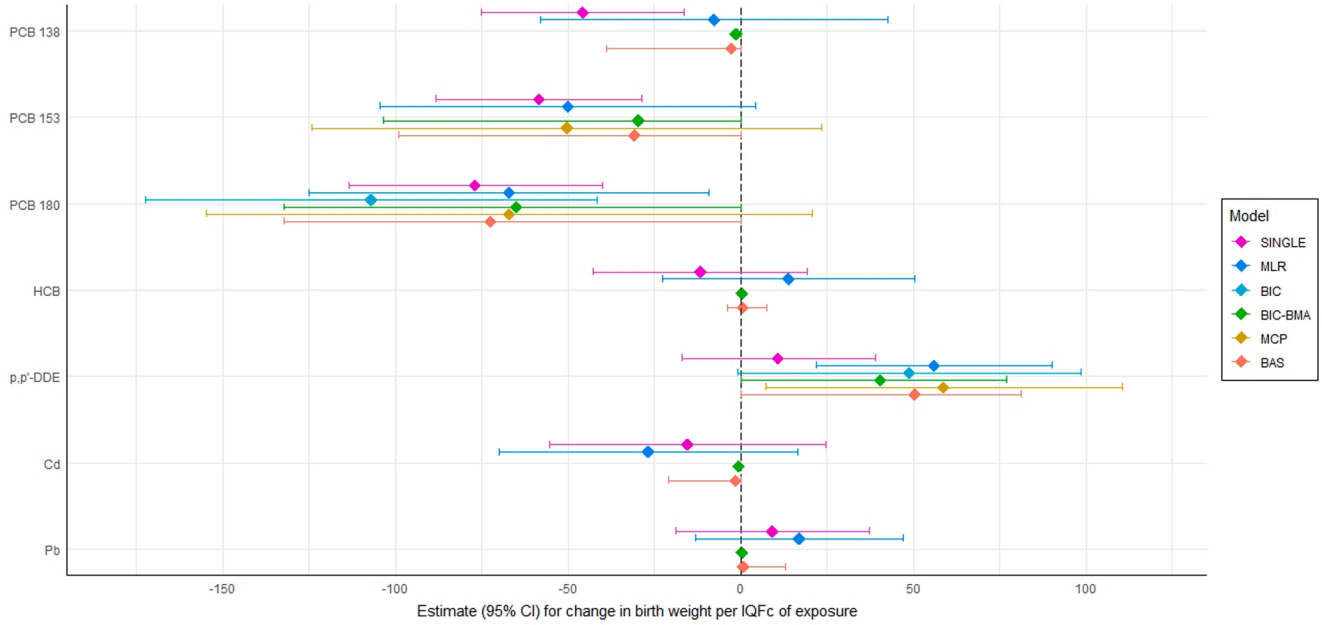

Fig. 3. Estimated association between the exposure biomarkers and birth weight from the single pollutant models (SINGLE) and five different multiple-exposure models (MLR, BIC, BIC-BMA, MCP, BAS) for birth weight. Estimate (95% CI) represents the change in mean birth weight (g) per IQFc of the exposure biomarker levels in the model adjusted for the other exposures (not for SINGLE), gestational age (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy and cohort. For BIC and MCP estimates are only obtained for the exposure markers retained after variable selection. 95% confidence intervals for refitted models after variable selection for the BIC and MCP approaches were adjusted for model selection. Abbreviations: PCB, polychlorinated biphenyl; HCB, hexachlorobenzene; *p,p'*-DDE, dichlorodiphenyldichloroethylene; Cd, cadmium; Pb, lead; IQFc, interquartile fold change; CI, confidence/credible interval; SINGLE, single pollutant regression model; MLR, multiple linear regression; BIC, Bayesian Information Criterion; BIC-BMA, Bayesian model averaging approach using BIC; MCP, minimax concave penalty; BAS, Bayesian Adaptive Sampling.

and birth outcomes and hormones seem to differ by molecular weight of the PCB congeners. However, it remains difficult to truly separate the effects of individual PCBs in observational studies given the high correlations between the individual PCBs. The positive association between cord blood concentration of *p,p'*-DDE and birth weight was also reported in several other recent studies (Cabrera-Rodriguez et al., 2018; Xu et al., 2017). Moreover, other studies showed that *p,p'*-DDE levels were associated with infant growth, showing a higher BMI at the age of 2 years old (Coker et al., 2018; Iszatt et al., 2015).

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). In addition, PCBs and their metabolites bind to thyroid transport proteins, such as transthyretin, displace thyroxine, and disrupt thyroid function (Duntas and Stathatos, 2015). Epidemiological studies have described mainly negative associations between PCB congeners and maternal and fetal thyroid hormones (Maervoet et al., 2007). DDE has been shown to inhibit androgens from binding to their receptors (Kelce et al., 1995). DDT and its metabolites have also been confirmed as thyroid-disrupting chemicals through human epidemiological studies (de Cock et al., 2014).

The interplay of the different endocrine disrupting compounds (EDCs) and their metabolites is not fully understood. They may interfere with fetal growth by acting on maternal metabolism, on the placenta or directly on fetal organs. Developmental and maternal hypothyroidism are associated with low birth weight and human development (Forhead and Fowden, 2014). The placenta is an endocrine organ itself and plays a major regulatory role in maintaining pregnancy and growth of the fetus. Estrogens and androgens play important roles in regulating nutrient delivery to the fetus as well as organ maturation (Baud and Berkane, 2019). As pregnancy progresses, and the fetus begins to produce hormones on its own, the endocrine disrupting effects of these compounds that have been noted in the mother may occur in the fetus as well (Fudvoye et al., 2014). Additionally, there is strong evidence indicating that estrogenic EDCs can program gene activity via epigenetic changes during critical periods in development, with long-term consequences that impact the health status of the individual throughout the remainder of life (Forhead and Fowden, 2014). Thyroid hormone and estrogenic chemicals modulate adipocyte development and activity which display receptors for these chemicals (Forhead and Fowden, 2014).

The strength of this study was that by pooling the data, power was increased to look into the association between multiple correlated pollutants and birth weight. This resulted in a dataset of 1579 individuals having measurements for PCB 138, PCB 153, PCB 180, *p,p'*-DDE, HCB, lead and cadmium. The four birth cohorts were obtained by subsequent sampling over a 10 years' time period in the Flemish region of Belgium, which could be seen as a homogeneous population. Moreover, the same sampling procedures have been followed and the same laboratories analyzed the pollutants across the four birth cohorts, and the analytical methods of these compounds were comparable over time. Blind samples of previous FLEHS campaigns were reanalyzed in the next FLEHS campaign, for which the results were comparable. As the mothers gave birth between 2002 and 2015, exposure to the selected compounds could have changed over time, i.e. changes in behaviors or manufacturing practices that could have reduced exposure or differences in correlation patterns over time, and this might have affected the analyses. This decline in exposure was observed in the three successive FLEHS studies for all studied exposures as published in Schoeters et al. (2017). There was however no significant interaction between cohort and the exposure–response associations, and the direction of the estimates (except for PCB 180 in 3xG) was in all cohorts the same. Furthermore, we cannot exclude the possibility of unmeasured confounding, both by other exposures and covariates. We used modeling techniques to select between collinear exposures. However, we were limited to the exposures measured in all four birth cohorts. As such, we did not test for co-exposure to other POPs from similar sources. Although

the multipollutant techniques that we used could also be used to investigate interaction between exposures and with covariates, we refrained from doing so because of the low power and potential adverse effects on estimating main effects. However this was assessed through single pollutant regression models. Another limitation could be that cadmium in cord blood may not be a very good indicator, as cadmium does not easily cross the placenta. Cd in maternal blood (even after birth) would have been better as indicator (Govarts et al., 2016). Moreover, smoking status during pregnancy was derived from questionnaire information and could be underreported.

5. Conclusions

In the pooled analysis of four Flemish birth cohorts we found that accounting simultaneously for the association of multiple pollutants with birth weight revealed new insights into the interplay of chemical exposure and the association with a certain health effect. Our results add to the existing evidence on detrimental effects of PCBs on birth weight and indicate a possible increase in birth weight due to *p,p'*-DDE (while correcting for PCBs). Assessing health risk of combinations of exposure biomarkers reflects better real-world situations. The findings allow more effective risk assessment as addressing the critical chemical in a mixture of pollutants is pivotal for risk assessment.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106149.

References

Agier, L., Portengen, L., Chadeau-Hyam, M., Basagaña, X., Giorgis-Allemand, L., Siroux, V., et al., 2016. A systematic comparison of linear regression–based statistical methods to assess exposome-health associations. Environ. Health Perspect. 124, 1848–1856.

Baeyens, W., Vrijens, J., Gao, Y., Croes, K., Schoeters, G., Den Hond, E., et al., 2014. Trace metals in blood and urine of newborn/mother pairs, adolescents and adults of the flemish population (2007–2011). Int. J. Hyg. Environ. Health 217, 878–890.

Barbieri, M.M., Berger, J.O., 2004. Optimal predictive model selection. Ann. Statist. 32, 870–897.

Barker, D.J., 1998. In utero programming of chronic disease. Clin. Sci. (Lond) 95, 115–128.

Baud, O., Berkane, N., 2019. Hormonal changes associated with intra-uterine growth restriction: Impact on the developing brain and future neurodevelopment. Front. Endocrinol. (Lausanne) 10, 179.

Béranger, R., Hardy, E.M., Binter, A.C., Charles, M.A., Zaros, C., Appenzeller, B.M.R., et al., 2020. Multiple pesticides in mothers' hair samples and children's measurements at birth: Results from the french national birth cohort (elfe). Int. J. Hyg. Environ. Health 223, 22–33.

Berk, R., Brown, L., Buja, A., Zhang, K., Zhao, L., 2013. Valid post-selection inference. Ann Statist 41, 802–837.

Berkowitz, G.S., Lapinski, R.H., Wolff, M.S., 1996. The role of dde and polychlorinated biphenyl levels in preterm birth. Arch. Environ. Contam. Toxicol. 30, 139–141.

Bobb, J.F., Valeri, L., Claus Henn, B., Christiani, D.C., Wright, R.O., Mazumdar, M., et al., 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics (Oxford, England) 16, 493–508.

Breheny, P., Huang, J., 2011. Coordinate descent algorithms for nonconvex penalized regression, with applications to biological feature selection. Ann Appl Stat 5, 232–253.

Cabrera-Rodriguez, R., Luzardo, O.P., Gonzalez-Antuna, A., Boada, L.D., Almeida-Gonzalez, M., Camacho, M., et al., 2018. Occurrence of 44 elements in human cord blood and their association with growth indicators in newborns. Environ. Int. 116, 43–51.

Casas, M., Nieuwenhuijsen, M., Martinez, D., Ballester, F., Basagana, X., Basterrechea, M., et al., 2015. Prenatal exposure to pcb-153, p, p'-dde and birth outcomes in 9000 mother-child pairs: Exposure-response relationship and effect modifiers. Environ. Int. 74, 23–31.

Chadeau-Hyam, M., Campanella, G., Jombart, T., Bottolo, L., Portengen, L., Vineis, P., et al., 2013. Deciphering the complex: Methodological overview of statistical models to derive omics-based biomarkers. Environ. Mol. Mutagen 54, 542–557.

Chiu, Y.H., Bellavia, A., James-Todd, T., Correia, K.F., Valeri, L., Messerlian, C., et al., 2018. Evaluating effects of prenatal exposure to phthalate mixtures on birth weight: A comparison of three statistical approaches. Environ. Int. 113, 231–239.

Claeskens, G., 2016. Statistical model choice. Annu. Rev. Stat. Appl. 3, 233–256.

Clyde, M.A., 2020. Bas: Bayesian variable selection and model averaging using bayesian adaptive sampling. R package version 1 (5), 5.

Cohen, L., Jefferies, A., 2019. Environmental exposures and cancer: Using the precautionary principle. Ecancermedicalscience 13 (ed91).

Coker, E., Chevrier, J., Rauch, S., Bradman, A., Obida, M., Crause, M., et al., 2018. Association between prenatal exposure to multiple insecticides and child body weight and body composition in the vhembe south african birth cohort. Environ. Int. 113, 122–132.

Covaci, A., Voorspoels, S., 2005. Optimization of the determination of polybrominated diphenyl ethers in human serum using solid-phase extraction and gas chromatography-electron capture negative ionization mass spectrometry. J. Chromatogr. B 827, 216–223.

de Cock, M., de Boer, M.R., Lamoree, M., Legler, J., van de Bor, M., 2014. Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants - a dutch prospective cohort study. Environ. Health 13, 106.

De Craemer, S., Croes, K., van Larebeke, N., Sioen, I., Schoeters, G., Loots, I., et al., 2016. Investigating unmetabolized polycyclic aromatic hydrocarbons in adolescents' urine as biomarkers of environmental exposure. Chemosphere 155, 48–56.

Den Hond, E., Govarts, E., Bruckers, L., Schoeters, G., 2009. Determinants of polychlorinated aromatic hydrocarbons in serum in three age classes–methodological implications for human biomonitoring. Environ. Res. 109, 495–502.

Duntas, L.H., Stathatos, N., 2015. Toxic chemicals and thyroid function: Hard facts and lateral thinking. Rev. Endocr. Metab. Disord 16, 311–318.

Eggesbo, M., Stigum, H., Longnecker, M.P., Polder, A., Aldrin, M., Basso, O., et al., 2009. Levels of hexachlorobenzene (hcb) in breast milk in relation to birth weight in a norwegian cohort. Environ. Res. 109, 559–566.

Flor, S., He, X., Lehmler, H.J., Ludewig, G., 2016. Estrogenicity and androgenicity screening of pcb sulfate monoesters in human breast cancer mcf-7 cells. Environ. Sci. Pollut. Res. Int. 23, 2186–2200.

Forhead, A.J., Fowden, A.L., 2014. Thyroid hormones in fetal growth and prepartum maturation. J. Endocrinol. 221, R87–r103.

Fudvoye, J., Bourguignon, J.P., Parent, A.S., 2014. Endocrine-disrupting chemicals and human growth and maturation: A focus on early critical windows of exposure. Vitam. Horm. 94, 1–25.

Gladen, B.C., Shkiryak-Nyzhnyk, Z.A., Chyslovska, N., Zadorozhnaja, T.D., Little, R.E., 2003. Persistent organochlorine compounds and birth weight. Ann. Epidemiol. 13, 151–157.

Govarts, E., Nieuwenhuijsen, M., Schoeters, G., Ballester, F., Bloemen, K., de Boer, M., et al., 2012. Birth weight and prenatal exposure to polychlorinated biphenyls (pcbs) and dichlorodiphenyldichloroethylene (dde): A meta-analysis within 12 european birth cohorts. Environ. Health Perspect. 120, 162–170.

Govarts, E., Remy, S., Bruckers, L., Den Hond, E., Sioen, I., Nelen, V., et al., 2016. Combined effects of prenatal exposures to environmental chemicals on birth weight. Int. J. Environ. Res. Public Health 13.

Govarts, E., Iszatt, N., Trnovec, T., de Cock, M., Eggesbo, M., Palkovicova Murinova, L., et al., 2018. Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: Pooled analysis of seven european birth cohorts. Environ. Int. 115, 267–278.

Guo, J., Wu, C., Qi, X., Jiang, S., Liu, Q., Zhang, J., et al., 2017. Adverse associations between maternal and neonatal cadmium exposure and birth outcomes. Sci. Total Environ. 575, 581–587.

Hoeting, J.A., Madigan, D., Raftery, A.E., Volinsky, C.T., 1999. Bayesian model averaging: A tutorial. Statist Sci 14, 382–417.

Iszatt, N., Stigum, H., Verner, M.A., White, R.A., Govarts, E., Murinova, L.P., et al., 2015. Prenatal and postnatal exposure to persistent organic pollutants and infant growth: A pooled analysis of seven european birth cohorts. Environ. Health Perspect. 123, 730–736.

Kalloo, G., Wellenius, G.A., McCandless, L., Calafat, A.M., Sjodin, A., Romano, M.E., et al., 2020. Exposures to chemical mixtures during pregnancy and neonatal outcomes: The home study. Environ. Int. 134, 105219.

Kelce, W.R., Stone, C.R., Laws, S.C., Gray, L.E., Kemppainen, J.A., Wilson, E.M., 1995. Persistent ddt metabolite p, p'-dde is a potent androgen receptor antagonist. Nature 375, 581–585.

Khanjani, N., Sim, M., 2006. Maternal contamination with dichlorodiphenyltrichloroethane and reproductive outcomes in an australian population. Environ. Res. 101, 373–379.

Kippler, M., Tofail, F., Gardner, R., Rahman, A., Hamadani, J.D., Bottai, M., et al., 2012. Maternal cadmium exposure during pregnancy and size at birth: A prospective cohort study. Environ. Health Perspect. 120, 284–289.
Kleinbaum, D.G., Kupper, L.L., Nizam, A., Rosenerg, E.S., 2013. Applied regression analysis and other multivariable methods, 5th ed. Cengage Learning, Boston.
Lauritzen, H.B., Larose, T.L., Oien, T., Sandanger, T.M., Odland, J.O., van de Bor, M., et al., 2017. Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: A scandinavian case-cohort study. Pediatr. Res. 81, 33–42.
Lee, S., Hong, Y.C., Park, H., Kim, Y., Ha, M., Ha, E., 2020. Combined effects of multiple prenatal exposure to pollutants on birth weight: The mothers and children's environmental health (moceh) study. Environ. Res. 181, 108832.
Lenters, V., Portengen, L., Smit, L.A., Jonsson, B.A., Giwercman, A., Rylander, L., et al., 2015. Phthalates, perfluoroalkyl acids, metals and organochlorines and reproductive function: A multipollutant assessment in greenlandic, polish and ukrainian men. Occup. Environ. Med. 72, 385–393.
Lenters, V., Vermeulen, R., Portengen, L., 2018. Performance of variable selection methods for assessing the health effects of correlated exposures in case–control studies. Occup. Environ. Med. 75, 522–529.
Liang, F., Paulo, R., Molina, G., Clyde, M.A., Berger, J.O., 2008. Mixtures of g priors for bayesian variable selection. J. Am. Stat. Assoc. 103, 410–423.
Lignell, S., Aune, M., Darnerud, P.O., Hanberg, A., Larsson, S.C., Glynn, A., 2013. Prenatal exposure to polychlorinated biphenyls (pcbs) and polybrominated diphenyl ethers (pbdes) may influence birth weight among infants in a swedish cohort with background exposure: A cross-sectional study. Environ Health 12, 44.
Longnecker, M.P., Klebanoff, M.A., Brock, J.W., Guo, X., 2005. Maternal levels of polychlorinated biphenyls in relation to preterm and small-for-gestational-age birth. Epidemiology 16, 641–647.
Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., et al., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ. Health Perspect. 112, 1691–1696.
Maervoet, J., Vermeir, G., Covaci, A., Van Larebeke, N., Koppen, G., Schoeters, G., et al., 2007. Association of thyroid hormone concentrations with levels of organochlorine compounds in cord blood of neonates. Environ. Health Perspect. 115, 1780–1786.
Martínez, M.A., Rovira, J., Sharma, R.P., Schuhmacher, M., Kumar, V., 2020. Reconstruction of phthalate exposure and dinch metabolites from biomonitoring data from the exhes cohort of tarragona, spain: A case study on estimated vs reconstructed dehp using the pbpk model. Environ. Res. 186, 109534.
Mughal, B.B., Fini, J.B., Demeneix, B.A., 2018. Thyroid-disrupting chemicals and brain development: An update. Endocr Connect 7, R160–r186.
Parent, A.-S., Naveau, E., Gerard, A., Bourguignon, J.-P., Westbrook, G.L., 2011. Early developmental actions of endocrine disruptors on the hypothalamus, hippocampus, and cerebral cortex. J. Toxicol. Environ. Health 14, 328–345.
Patel, J.F., Hartman, T.J., Sjodin, A., Northstone, K., Taylor, E.V., 2018. Prenatal exposure to polychlorinated biphenyls and fetal growth in british girls. Environ. Int. 116, 116–121.
Philippat, C., Heude, B., Botton, J., Alfaidy, N., Calafat, A.M., Slama, R., 2019. Prenatal exposure to select phthalates and phenols and associations with fetal and placental weight among male births in the eden cohort (france). Environ. Health Perspect. 127, 17002.
Rovira, J., Martínez, M., Sharma, R.P., Espuis, T., Nadal, M., Kumar, V., et al., 2019. Prenatal exposure to pfos and pfoa in a pregnant women cohort of catalonia, spain. Environ. Res. 175, 384–392.
Schoeters, G., Govarts, E., Bruckers, L., Den Hond, E., Nelen, V., De Henauw, S., et al., 2017. Three cycles of human biomonitoring in flanders - time trends observed in the flemish environment and health study. Int. J. Hyg. Environ. Health 220, 36–45.
Schroijen, C., Baeyens, W., Schoeters, G., Den Hond, E., Koppen, G., Bruckers, L., et al., 2008. Internal exposure to pollutants measured in blood and urine of flemish adolescents in function of area of residence. Chemosphere 71, 1317–1325.
Schwarz, G., 1978. Estimating the dimension of a model. Ann. Statist. 6, 461–464.
Shah, R.D., Samworth, R.J., 2013. Variable selection with error control: Another look at stability selection. J. Royal Statist. Soc. Series B (Statist. Methodol.) 75, 55–80.
Stafoggia, M., Breitner, S., Hampel, R., Basagana, X., 2017. Statistical approaches to address multi-pollutant mixtures and multiple exposures: The state of the science. Curr. Environ. Health Rep. 4, 481–490.
Sun, Z., Tao, Y., Li, S., Ferguson, K.K., Meeker, J.D., Park, S.K., et al., 2013. Statistical strategies for constructing health risk models with multiple pollutants and their interactions: Possible choices and comparisons. Environ. Health 12, 85.
Tang, M., Yin, S., Zhang, J., Chen, K., Jin, M., Liu, W., 2018. Prenatal exposure to polychlorinated biphenyl and umbilical cord hormones and birth outcomes in an island population. Environ. Pollut. 237, 581–591.
UBA, 2014. Mixtures in the environment - development of assessment strategies for the regulation of chemicals under reach. Environmental Research of the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety.
Vafeiadi, M., Vrijheid, M., Fthenou, E., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., et al., 2014. Persistent organic pollutants exposure during pregnancy, maternal gestational weight gain, and birth outcomes in the mother-child cohort in crete, greece (rhea study). Environ. Int. 64, 116–123.
Vizcaino, E., Grimalt, J.O., Fernández-Somoano, A., Tardon, A., 2014. Transport of persistent organic pollutants across the human placenta. Environ. Int. 65, 107–115.
Wolff, M.S., Engel, S., Berkowitz, G., Teitelbaum, S., Siskind, J., Barr, D.B., et al., 2007. Prenatal pesticide and pcb exposures and birth outcomes. Pediatr. Res. 61, 243–250.
Woods, M.M., Lanphear, B.P., Braun, J.M., McCandless, L.C., 2017. Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: A bayesian analysis of the home study. Environ Health 16, 115.
Xu, C., Yin, S., Tang, M., Liu, K., Yang, F., Liu, W., 2017. Environmental exposure to ddt and its metabolites in cord serum: Distribution, enantiomeric patterns, and effects on infant birth outcomes. Sci. Total Environ. 580, 491–498.
Zellner, A., Siow, A., 1980. Posterior odds ratios for selected regression hypotheses. Trabajos de Estadistica Y de Investigacion Operativa 31, 585–603.
Zou, H., Hastie, T., 2005. Regularization and variable selection via the elastic net. J R Stat. Soc. Ser. B Stat. Methodol. 67, 301–320.