Environment International 195 (2025) 109225

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Influence of prenatal hexachlorobenzene, PCB and selenium levels on growth trajectories in the first year of life: Findings from the NEHO birth cohort

Ilaria Cosentini [a,1,*], Silvia Ruggieri [a,1], Paolo Colombo [a], Fabrizio Bianchi [b], Liliana Cori [b], Melania Casella [a], Elisa Eleonora Tavormina [a], Fabio Cibella [a], Gaspare Drago [a]

[a] National Research Council of Italy, Institute for Biomedical Research and Innovation, Palermo, Italy
[b] National Research Council of Italy, Institute of Clinical Physiology, Pisa, Italy

ARTICLE INFO

Keywords:
Hexachlorobenzene
Organochlorine pesticides
Polychlorobiphenyls
Endocrine-disrupting chemicals
Essential elements
Infant growth trajectories
Birth cohort

ABSTRACT

Prenatal exposure to endocrine-disrupting chemicals (EDCs) may impact postnatal growth trajectories, increasing the risk of various diseases later in life. This issue is of particular concern in industrially contaminated areas, where environmental matrices contain mixtures of pollutants. This study aimed to evaluate the associations between cord serum concentrations of organochlorine pollutants (hexachlorobenzene-HCB and polychlorinated biphenyls-PCBs) and essential elements (EEs), and weight growth trajectories during the first year of life. We analyzed data from 237 infants enrolled in the Neonatal Environment and Health Outcomes (NEHO) cohort. Using the Group-Based Multivariate Trajectory modeling approach, we identified three distinct growth trajectories from birth to 12 months, classified as "Higher," "Normal," and "Lower." Multinomial regression models were then applied to the whole sample and stratified by sex to assess the associations between individual exposures and the identified child growth trajectories. HCB exposure was associated with an increased risk of reduced growth during the first year of life in both the overall sample and among males [higher vs normal: OR_{Male} = 0.33 (95 % CI_{Male}:0.12;0.87); lower vs normal: OR_{Male} = 2.17 (95 % CI_{Male}:0.94;5.00)]. Conversely, PCB-180 exposure was linked to higher growth only in females [higher vs normal: OR_{Female} = 24.10 (95 % CI_{Female}:1.33;438.24)]. Elevated levels of selenium in cord serum were negatively associated with excessive growth [higher vs normal: $OR_{Overall}$ = 0.50 (95 % $CI_{Overall}$: 0.26;0.97)]. These findings suggest sex-specific effects on the growth profile during the first year of life, with different chemical exposures contributing to different outcomes.

1. Introduction

Adequate growth during fetal development and over the first twelve months of life can provide a solid foundation for an individual's long-term health (Adair et al., 2013; Singhal, 2017). Indeed, both excessive and inadequate growth during these critical periods are associated with an increased risk for multiple diseases in adulthood, including obesity and its related comorbidities such as hypertension, cardiovascular diseases, diabetes, and cancer (Oshiro et al., 2022; Cauzzo et al., 2023; Moschonis et al., 2023). Referring only to dysmetabolic diseases, the Global Burden of Disease 2019 report estimated that over 500,000 deaths in EU countries were linked to obesity (GBD 2019 Risk Factors Collaborators, 2020). This has led to the prioritization of the fight against obesity, promoted by WHO (World Health Organization)/

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criterion Value; BMI, Body Mass Index; BKMR, Bayesian Kernel Machine Regression; cAIC, Consistent AIC; DAG, Directed Acyclic Graph; DOHaD, Developmental Origins of Health and Disease; EDCs, Endocrine-Disrupting Chemicals; EEs, Essential Elements; EM, Expectation Maximization; GBD, Global Burden of Disease; GBMT, Group-Based Multivariate Trajectory Model; HCB, Hexachlorobenzene; HQIC, Hannan-Quinn Information Criterion; NEHO, Neonatal Environment and Health Outcomes; NPCSs, National Priority Contaminated Sites; OCs, Organochlorine Pesticides; PCBs, Polychlorinated Biphenyls; PIP, Posterior Inclusion Probabilities; POPs, Persistent Organic Pollutants; ssBIC, Sample Size-Aadjusted Bayesian Information Criterion; TNC, Trans-Nonachlor; WHO, World Health Organization.

* Corresponding author.
E-mail address: ilaria.cosentini@irib.cnr.it (I. Cosentini).

[1] Both Authors equally contributed to the manuscript.

https://doi.org/10.1016/j.envint.2024.109225
Received 10 July 2024; Received in revised form 16 December 2024; Accepted 17 December 2024
Available online 20 December 2024

Europe within the Non-Communicable Disease Agenda, emphasizing the importance of prevention actions starting from the periconceptional period (WHO-a, 2017; WHO-b, 2022).

During intrauterine development, fetal cells and tissues are primed to adapt to external environmental challenges. Alterations or disruptions in these developmental processes can result in a mismatch between prepared fetal responses and the external environment encountered after birth. Such discrepancies can have significant implications, leading to a metabolic-susceptible phenotype (Sargis, Heindel and Padmanabhan, 2019). Since environmental pollutants can disrupt fetal developmental processes and induce lasting changes in metabolic profiles, mitigating environmental exposures is critical during pregnancy (Svensson et al., 2021). Among environmental factors, persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and dichlorodiphenyldichloroethylene (p,p'-DDE), have been shown to disrupt fetal development, largely through hormonal dysregulation (Bonefeld-Jørgensen et al., 2014) and oxidative stress (Kumar et al., 2014). Both can alter placental physiology, affecting nutrient transfer to the fetus and maternal-fetal metabolic communication (Krönke et al., 2022; Yan et al., 2023). The number of studies examining the link between exposure to POPs and early-life growth trajectories has risen significantly. However, despite extensive research on pollutants such as PCBs, HCB, and p,p'-DDE, findings remain inconsistent, with no clear consensus (Cai et al., 2023; Montazeri et al., 2023; Stratakis et al., 2022; Delvaux et al., 2014; Tang-Péronard et al., 2014; Garced et al., 2012).

Selenium (Se) plays a protective role against oxidative damage, and Se deficiency is linked to adverse pregnancy outcomes such as preterm birth and pre-eclampsia (Al-Kunani et al., 2001; Rayman et al., 2014; Duntas, 2020). Similarly, imbalances in copper (Cu) and zinc (Zn) during pregnancy can impair fetal growth through inflammation and oxidative stress (Lewandowska et al., 2019; Gohari et al., 2023). Moreover, all three essential elements (EEs) play crucial roles in thyroid hormone metabolism (Wu et al., 2021).

Nevertheless, evidence on the role of essential element levels during pregnancy and their impact on growth trajectories is limited (Zhou et al., 2024; Mehta et al., 2023), with most research focusing on immediate birth outcomes or fetal growth rather than postnatal development patterns (Atazadegan et al., 2022).

Monitoring growth curves is crucial for the early identification of potential health problems, enabling timely intervention and treatment. Early growth patterns can also predict long-term health effects in adulthood. Understanding both how prenatal exposure to toxicants can modify growth trajectories and the possible differences between sexes is fundamental to develop effective preventive measures.

In addition to the sex differences in physical growth between infant males and females, sex-specific adaptive responses to environmental factors may originate from differences in xenobiotic metabolism and gene expression. Furthermore, estrogen and androgen signaling pathways are among the most well-documented targets of endocrine-disrupting chemicals (EDCs) (Amir et al., 2021), which can lead to different levels of susceptibility to environmental stressors (Cho, Holditch-Davis and Miles, 2010).

Thus, our main aim was to test whether early exposure to environmental challenges, such as EE availability and exposure to chemical contaminants during intrauterine development, affects weight growth trajectories in the first year of life, taking into account potential sex-specific effects.

To this end, we evaluated the growth trajectories during the first year of life of infants enrolled in the Neonatal Environment and Health Outcomes (NEHO) birth cohort (Ruggieri et al., 2021; Drago et al., 2023). The NEHO cohort includes mothers living in 3 out of 42 Italian industrially contaminated sites legally designated as National Priority Contaminated Sites (NPCSs) for environmental remediation. Milazzo-Valle del Mela (referred to as Milazzo) and Augusta-Priolo (referred to as Priolo) are active petrochemical plant located in eastern Sicily, while in the Crotone area in the region of Calabria the most relevant environmental impact is due to three disused industrial areas (Ruggieri et al., 2019). In these areas, previous studies have reported PCB, HCB, and heavy metal contamination in all the environmental matrices, including food chain (Maisano et al., 2016; Traina et al., 2021; Oliveri et al., 2022). Additionally, growth trajectories were associated with prenatal exposure to different EDCs and EEs levels in order to identify health impacts of prenatal exposure over the life course.

2. Materials and methods

2.1. Study population

This study included a subsample of 237 (NEHO subset) out of 845 mother–child pairs enrolled in the NEHO residential birth cohort (Ruggieri et al., 2019) for which measures of 17 umbilical cord

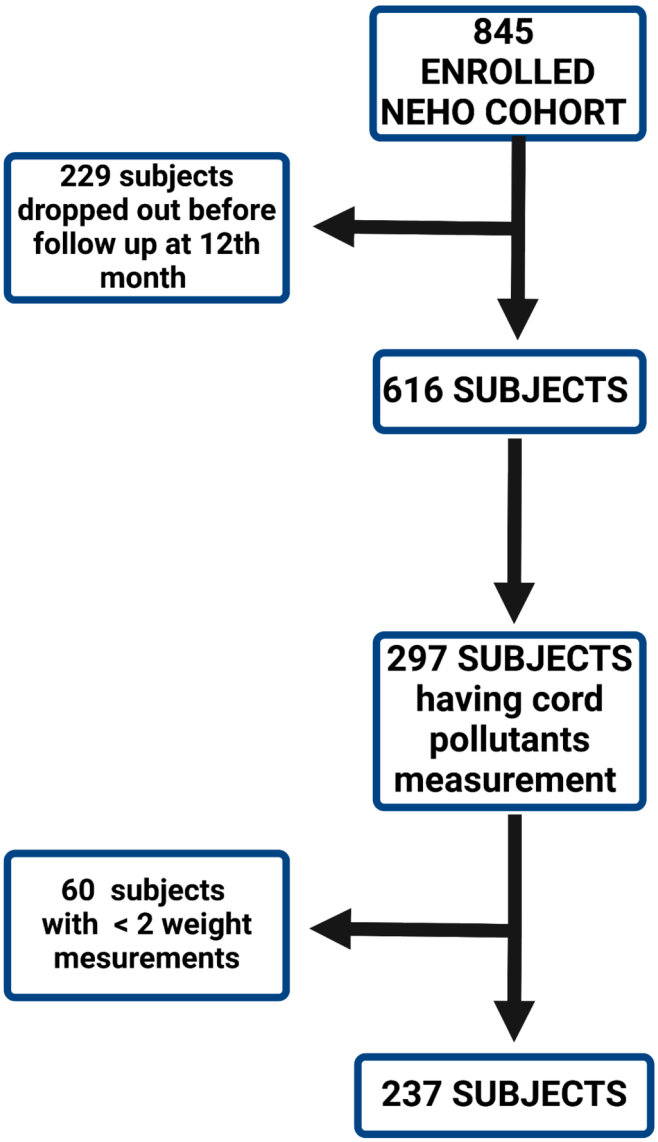

Fig. 1. Subject selection for the analysis. The chart shows the selection criteria for the total sample. 845 mothers were initially enrolled in the NEHO cohort. The twelve-month questionnaires were filled out by 616. A subset of these mothers, including 237 subjects, has a set of 17 cord analyte measurements. Additionally, 60 subjects were excluded from the analysis for having less than two weight measurements during the first year of life. Created with BioRender.com.

chemicals were available. Detailed information about the subjects analyzed are provided below and in Fig. 1. Pregnant women were enrolled during the third trimester of pregnancy in three different NPCSs (Crotone, Milazzo and Priolo NPCSs) and their surrounding areas. All 237 children were born at full-term. Mothers and their children were evaluated at birth and followed up at 6 and 12 months of age.

Soon after birth, perinatal information was recorded by trained medical personnel. During follow-up, socio-demographic characteristics and anthropometric data were collected by means of web-based questionnaires filled out by the mothers including a diary for monthly measurements of children's weight.

2.2. Sample collection

Cord blood was drawn immediately after delivery. Blood tubes were stored at 4 °C and centrifuged within 24 h. After serum separation, samples were temporarily stored at − 20 °C in each maternity unit and then transported on dry ice to the NEHO biobank for long-term storage at − 80 °C.

2.3. Exposure assessment

POPs were analyzed at the National Institute for Health and Welfare, Chemical Exposure Unit, in Kuopio, Finland, using an Agilent 7000B gas chromatograph triple quadrupole mass spectrometer (GC–MS/MS). Inorganic trace elements were measured at the micropollutant unit laboratory of LERES (Laboratoire d'Etude et de Recherche en Environnement et Santé) at the French School of Public Health − EHESP (Rennes, France) with a plasma inductive system coupled with tandem mass spectrometry detection (ICP-MS/MS). Detailed analytical procedures have been previously described (Longo et al., 2022; Drago et al., 2023).

Cord serum concentrations of 17 analytes were considered: three EEs (Se, Zn, and Cu), arsenic (As), mercury (Hg), three different organochlorine pesticides (OCs: HCB, Trans-Nonachlor TNC, p'p'-DDE) and nine PCBs (PCB-74, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, PCB-187). For this study, we opted to use the limits of quantification (LOQs) rather than the limits of detection (LODs) to ensure the accuracy and precision of our measurements. This choice allows for reliable quantification of substance levels, minimizing uncertainty and providing robust data suitable for our analyses. Concentrations below LOQ were substituted with a value equal to LOQ divided by 2, according to Montazeri et al. (2023). Due to their skewed distribution, the concentrations were log-transformed and a standard normal variate (SNV) normalization was performed. Chemicals with more than 10 % substituted values were excluded from further analysis.

2.4. Ethics approvall

The study followed the Declaration of Helsinki. All procedures were compliant with the General Data Protection Regulation (UE 2016/679) and Italian laws on data protection. To this aim, all questionnaire data and biological samples were pseudonymized using ID tracking numbers. The study was approved by the relevant Ethics Committees (for Milazzo NPCS, the Ethics Committee of the University Hospitals of Messina, September 18, 2017, n. 9/2017; for Priolo NPCS, the Ethics Committee "Catania 2", July 11, 2017, n. 38/2017/CECT2; for Crotone NPCS, the Ethics Committee of the Calabria Region, July 20, 2017, n. 173).

2.5. Growth trajectories

Monthly measurements of each child's weight, from 0 to 12 months, were retrieved from clinical birth records and NEHO questionnaires. Specifically, birth weight was recorded at delivery, while data for subsequent weights were collected through two follow-up questionnaires at 6 and 12 months. Mothers were asked to report only the weight measured by their pediatrician during routine check-ups. Weights measured between 1st and 6th months were reported in the 6-month questionnaire, and the same procedure was used for the period between the 7th and 12th months.

A total of 1,608 wt measurements were collected over the first 12 months of life for 237 children (Fig. S1). Mothers reported an average of 6.8 wt measurements (±3.2 SD). Table S1 reports the number, mean (±SD) and median [Q1-Q3] of weight measurements reported from birth to 1 year of age.

Weight Z-scores were calculated separately for each child by sex, using subjects with complete data available (72 % of the 845 enrolled mother/child couples) from the entire NEHO cohort (N = 616). Finally, trajectories for weight Z-scores were estimated for 237 participants who reported at least two different weight measures between 0 and 12 months using a Group-Based Multivariate Trajectory model (GBMT). The GBMT is a latent class technique for analyzing growth curves and enables the estimation of missing values through the expectation–maximization (EM) algorithm (Nagin et al., 2018). A multivariate polynomial regression analysis was performed with respect to time as the "observed variable" to account for multiple continuous indicators. In this study, we explored latent groups of children following similar growth trajectories. The number of trajectories was selected using the best combination of the number of clusters with different growth (testing from 2 to 4) as well as the polynomial degree order (from 1 to 4) of the modeled trajectories. The smallest absolute Bayesian information criterion value (BIC), Akaike information criteria (AIC), consistent AIC (cAIC), Hannan-Quinn information criterion (HQIC), and Sample size-adjusted Bayesian information criterion (ssBIC) were used to select the best combination (Akaike, 1974; Bozdogan, 1987; Sclove, 1987). GBMT was performed using the "gbmt" R package (Magrini, 2022).

The obtained NEHO Z-scores were compared to WHO Child Growth Standards Z-scores retrieved using the R package "childsds" (WHO Child Growth Standards, 2006; Vogel, 2022).

Three different clusters of growth curves were thus identified and labeled: Cluster 1 as "Higher," Cluster 2 as "Normal," and Cluster 3 as "Lower.".

2.6. Covariates

A directed acyclic graph (DAG) was used to represent the connections between covariates based on the literature (Fig. S2). The variables included self-reported data on parent/child characteristics and behaviors, obtained either at enrollment or from follow-up questionnaires (6th and 12th months). The covariates were: maternal age (continuous, years), maternal prepregnancy and paternal weight (continuous, kg), smoking during pregnancy (binary, yes/no), folate supplementation during pregnancy (binary, yes/no), parity (binary, nulliparous/multiparous) and NPCS residence (Priolo, Crotone, Milazzo), collected at the enrollment. Breastfeeding during the first 6 months (binary, yes/no) was collected at 6th month follow-up. Other covariates were obtained from hospital records at delivery, including child sex (binary, male/female), type of delivery (binary, vaginal/caesarean), birth weight (continuous, g) and gestational age (continuous, weeks). Alcohol consumption during pregnancy was removed from the confounders list because of the limited number (n = 10; 4.3 %) of mothers who self-reported alcohol consumption during gestation.

2.7. Statistical analysis

Descriptive statistics were used to compare maternal and child characteristics, with 237 mothers included in the study sample. Qualitative maternal and child characteristics were reported as absolute and relative frequencies (N(%)). Median and interquartile range [Q1–Q3] were used to indicate continuous non-normally distributed variables. Significant differences between the NEHO and study samples were assessed by the Chi-square test for categorical variables and by the

Mann-Whitney *U* test for non-normally distributed continuous variables. For the three growth trajectories ("Higher", "Normal", "Lower"), the Chi-square test was used to assess differences in categorical variables and the Kruskall-Wallis test to identify differences in continuous (non-normally distributed) variables.

2.8. Exposure-growth trajectory associations

Associations between pollutant concentrations and growth trajectories were analyzed by running single exposure models using multinomial logistic regression. We performed two different multinomial regression models: Model 1 without confounder selection and Model 2 with stepwise confounder selection. In addition, a third model using the ridge penalty regression (Model 3) was generated. This regression approach aimed at reducing multicollinearity among independent variables. Moreover, the introduction of a penalty term is useful in the overfitting reduction. Multinomial regressions were performed using the "nnet" R package and the "MASS" R package for stepwise procedure (Venables and Ripley, 2013). The "MultBiplotR" R package was used for the multinomial ridge logistic regression (Vicente-Villardon, Vicente-Gonzalez and Frutos-Bernal, 2023). The best lambda term was identified by cross-validation using the "glmnet" R package (function "cv.glmnet") (Friedman, Hastie and Tibshirani, 2010). Models were corrected for the covariates described in the previous section. First, each cord pollutant and the sum of cord PCBs ($\sum PCB_{(138,153,180)}$) were tested as independent variables. $\sum PCB_{(138,153,180)}$ was computed summing the concentrations of PCB-138, PCB-180 and PCB-153 with less than 10 % substituted values.

Each regression model was replicated, stratified by sex, as sensitivity analysis. Two different outcomes were assessed in as many comparisons: "Higher vs Normal" and "Lower vs Normal" classes.

The beta coefficient estimates were exponentiated to odds ratios (ORs) and reported using a forest plot. Statistical significance was defined as a 95 % confidence interval (CI) level.

In addition, interaction analyses were performed to explore potential sex differences in the effects. For this, Model 1 and Model 2 were re-estimated, incorporating interaction terms between sex and each pollutant. Since the ridge regression analysis assumed the inclusion of all pollutants, the resulting model would have been complex considering the limited sample size. Thus, Model 3 was excluded from this analysis.

2.9. Bayesian Kernel Machine Regression

The Bayesian Kernel Machine Regression (BKMR) model was used to explore non-linear associations and interactions between *in utero* exposure and growth trajectories (Bobb et al., 2015). BKMR models provide a robust framework for assessing individual and joint effects within complex exposure mixtures. By exploring non-linear and interactive relationships, BKMR uncovers how pollutants influence health outcomes in combination. Bivariate exposure–response curves, generated while holding other exposures constant at key percentiles (e.g., 25th, 50th, 75th), help identify harmful pollutants and elements with potential protective effects. This approach is particularly valuable in examining synergistic or antagonistic relationships within exposure mixtures (Warner et al., 2018).

For this analysis, we subdivided the chemicals into non-overlapping groups: Group 1 included EEs (Se, Zn, Cu), Group 2p,p'-DDE and HCB, and Group 3 PCBs (PCB-138, PCB-153, PCB-180). The group-specific posterior inclusion probabilities (group-PIP) were calculated using hierarchical variable selection to evaluate the relative importance of each group for model inclusion. Additionally, within the selected groups, conditional-PIP estimated the likelihood of a particular exposure influencing the outcome within each group (Warner et al., 2018). PIP values range from 0 to 1; a threshold value > 0.50 for both group- and conditional-PIP was considered indicative of major contributor (Zuk, Liberda and Tsuji, 2021).

The BKMR model is typically used for continuous (Gaussian) and binary (binomial) outcomes, so is not directly applicable to multinomial outcomes. Thus, we adapted the BKMR approach by conducting two separate binary comparisons, "Higher vs Normal" and "Lower vs Normal," using the default parameters of the "bkmr" R package (Bobb et al., 2018) and fitting Markov Chain Monte Carlo (MCMC) chain with 10,000 iterations. All analyses were considered significant at a p level ≤ 0.05 and were conducted in R, version 4.3.1 (R Core Team, 2023).

Table S2 summarizes the main characteristics of the statistical methods used.

3. Results

One year after birth, 616 mothers from the total NEHO cohort reported information about their child. Our study focused on 237 of these individuals with available umbilical cord sample concentrations of 17 analytes. Table 1 reports the comparisons of socio-demographic and newborn characteristics between the study sample and the whole NEHO cohort, excluding the 237 evaluated subjects (N:845–237 = 608). No significant differences between the two groups were found, except for NPCS, educational level and delivery type. The NPCS distribution between study sample and NEHO cohort was significantly different with a lower percentage of mothers residing in the Priolo NPCS with respect to the whole NEHO cohort. A higher percentage of mothers having medium/high educational level is included in the study sample. Delivery type was statistically significant, outlining a higher number of vaginal births in the study sample (75.5 %). Concentrations of cord chemicals are listed in Table 2. Analyte concentrations across the three NPCSs are reported in Table S3.

Three different weight trajectories were identified by selecting a polynomial degree equal to two or quadratic according to the indicator. The value of the statistical indicator used to select the number of trajectories is reported in Fig. S3.

The "Higher" class (cluster 1) included 57 children whose weight trajectories, during the first year of life, were more than one standard deviation above the cohort mean. The "Lower" class (cluster 3) had the highest number of subjects (n = 97) and included children with a weight trajectory more than 0.5 standard deviations below the mean. Finally, 83 children were grouped in the "Normal" class (cluster 2). Fig. 2 shows the overall trajectories for each class.

Fig. S4A presents monthly NEHO Z-scores for the first year of life for individuals belonging to the same class. For comparison, Fig. S4B reports the Z-scores of the subjects with respect to the WHO Child Growth.

Table 3 shows the differences in socio-demographic, maternal, delivery and child characteristics among the three identified growth trajectory groups. Differences in NPCSs was statistically significant among the three classes: a large percentage of mothers residing in Priolo belonged to the "Normal" class (57.8 %), and a higher proportion of mothers residing in Crotone belonged to the "Higher" class (47.4 %). Mothers grouped in the "Higher" class presented a higher pre-pregnancy weight (64.0 [57.0–72.3]kg), followed by cluster 2 (60.0 [55.5–66.8]kg) and cluster 3 (57.0 [52.8–65.0]kg) ($p < 0.01$). Gestational age was statistically different across the three classes ($p = 0.035$), showing the highest value in the "Higher" class (40.0 [39.0–40.0]yrs). The frequency distribution of delivery type was significantly different among the three classes ($p = 0.034$). Child sex was not associated with the growth trajectories. Children belonging to the "Higher" class had a greater length at delivery, followed by the "Normal" and "Lower" classes ($p < 0.001$). A similar trend was observed for child weight at birth, 6, and 12 months (Table S4). Differences in NEHO Z-scores and WHO Z-scores for the three time points among the three classes were statistically significant ($p < 0.001$).

Differences in analyte concentrations among the three clusters are reported in Table 4. HCB was the unique element showing a significant difference in median concentrations among the three groups ($p = 0.004$).

Table 1
Parental and newborn characteristics of the study population. The p-value was computed between the whole NEHO cohort having subtracted the study sample (n = 608) and the study sample (n = 237). Categorical variables are reported as N(%). Continuous variables are presented as mean(SD) or median[Q1–Q3] as appropriate. Significant p-values are in bold.

	Study sample	NEHO	p-value
	n = 237	n = 608	
SOCIO-DEMOGRAPHIC CHARACTERISTICS			
	N(%)	N(%)	
NPCS[#]:			**<0.001**
PRIOLO	117 (49.4 %)	444(73.0 %)	
CROTONE	78 (32.9 %)	89(14.6 %)	
MILAZZO	42 (17.7 %)	75(12.3 %)	
Marital status[#]:			0.524
Married	154 (65.3 %)	380(62.6 %)	
Unmarried	82 (34.7 %)	227(37.4 %)	
Educational level[#]:			**<0.001**
High	76 (32.2 %)	133(22.0 %)	
Medium	129 (54.7 %)	293(48.4 %)	
Low	31 (13.1 %)	179(29.6 %)	
Type of Delivery[#]:			**<0.001**
Caesarean	58 (24.5 %)	255(41.9 %)	
Vaginal	179 (75.5 %)	353(58.1 %)	
Maternal folic acid supplementation[#]:			0.066
No	30 (12.7 %)	50(8.24 %)	
Yes	207 (87.3 %)	557 (91.8 %)	
Previous pregnancy[#]:			0.528
Nulliparous	119 (51.1 %)	247(53.9 %)	
Parous	114 (48.9 %)	211(46.1 %)	
Smoking during pregnancy[#]:			0.173
No	216 (91.5 %)	533(88.0 %)	
Yes	20 (8.5 %)	73(12.0 %)	
Alcohol consumption during pregnancy[#]:			0.870
No	225 (95.7 %)	573(95.2 %)	
Yes	10 (4.3 %)	29(4.82 %)	
	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	
Maternal age (years)[§]	31.0[28.0;34.0]	31.0 [27.0;34.2]	0.155
Maternal prepregnancy BMI (Kg/m^2)[§]	22.2[20.1;24.9]	22.5 [20.4;25.5]	0.474
Maternal weight gain (Kg)[§]	12.0[9.03;15.0]	12.0 [9.65;15.0]	0.337
Maternal prepregnancy weight (kg)[§]	60.0[54.0;68.0]	60.0 [53.1;68.0]	0.717
Paternal weight (kg)[§]	78.2[70.1;85.0]	80.0 [70.3;85.7]	0.237
Gestational age (weeks)[§]	39.0[39.0;40.0]	39.0 [38.0;40.0]	0.190
CHILD CHARACTERISTICS			
	N (%)	N (%)	
Child sex[#]:			0.250
Female	100 (42.2 %)	285 (46.9 %)	
Male	137 (57.8 %)	323 (53.1 %)	
	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	
Child weight at delivery(g)[§]	3340 [3050;3580]	3290 [3030;3550]	0.417
Child length at delivery(cm)[§]	50.0[49.0;51.0]	50.0 [49.0;51.0]	0.057

SD = standard deviation; [Q1-Q3] = [1st and 3rd quartile]; NPCS = National Priority Contaminated Site; BMI = Body Mass Index; Educational level categorized as "High" (degree or higher qualification), "Medium" (upper secondary school diploma), and "Low" (secondary school diploma or lower); [#] p values from Chi-squared test; [§] p values from Mann-Whitney *U* test.

Associations between individual cord analytes and growth trajectories, corrected for all the evaluated confounders and deriving from "Model 1," are shown in Fig. 3. The results for multinomial Model 1 are presented as separate forest plots for the "Higher" and "Lower" classes using "Normal" as reference. The analyses were performed for the total sample (in black) and stratified for sex (male in cyan and female in pink). Additionally, Fig. S5 presents the interaction coefficients from regressions of each exposure on growth trajectories, with sex as an interaction term.

Prenatal exposure to HCB was associated with a statistically significant reduction in risk of belonging to the "Higher" class, with a consequent higher probability of belonging to the "Lower" class in the total study sample [higher vs normal: HCB OR = 0.57 (95 %CI: 0.36; 0.92); lower vs normal: HCB OR = 1.64 (95 %CI: 1.05; 2.57)]. The results were confirmed in males [higher vs normal: HCB OR = 0.38 (95 %CI: 0.18;

Table 2
Cord serum chemical concentrations of the study population (N = 237).

CORD CHEMICALS	GEOM. MEAN (SD)	MEDIAN [Q1-Q3]	< LOQ (%)
Se (μg/L)	53.2 (10.4)	52.0 [47.0;58.0]	0
As (μg/L)	1.52 (2.68)	0.50 [0.50;1.30]	70.1
Hg (μg/L)	0.65 (0.77)	0.45 [0.20;0.84]	43.5
Zn (μg/L)	882 (154)	871 [775;955]	0
Cu (μg/L)	429 (208)	385 [310;485]	0
HCB (ng/L)	20.6 (19.0)	16.7 [11.3;23.6]	0
TNC (ng/L)	2.65 (0.86)	2.50 [2.50;2.50]	97.1
p'p'-DDE (ng/L)	134 (152)	94.0 [56.1;155]	0
PCB-74 (ng/L)	2.82 (1.47)	2.50 [2.50;2.50]	94.1
PCB-118 (ng/L)	4.78 (3.68)	2.50 [2.50;6.08]	62.4
PCB-138 (ng/L)	17.2 (14.8)	12.2 [8.37;19.7]	4.6
PCB-153 (ng/L)	28.8 (25.4)	21.4 [13.0;34.2]	0.8
PCB-156 (ng/L)	2.82 (1.31)	2.50 [2.50;2.50]	93.7
PCB-170(ng/L)	7.65 (7.99)	5.38 [2.50;9.46]	46.4
PCB-180 (ng/L)	18.6 (19.4)	12.7 [7.49;22.8]	9.7
PCB-183 (ng/L)	2.75 (1.23)	2.50 [2.50;2.50]	95.4
PCB-187 (ng/L)	5.62 (6.72)	2.50 [2.50;6.28]	67.5
$\sum PCB_{(138,153,180)}$	64.6 (58.9)	47.4 [29.3;75.3]	–

SD = standard deviation; [Q1-Q3] = [1st and 3rd quartile]; LOQ = limit of quantification. Chemicals with < 10 % LOQ were selected for the main analyses.

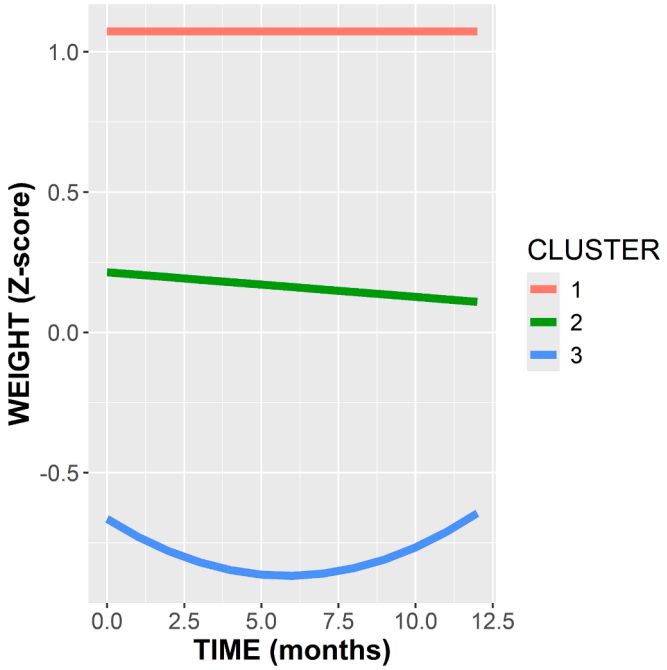

Fig. 2. Weight growth trajectories. Trajectories identified by group-based multivariate trajectory Expectation-Maximization model using the weight Z-scores of the NEHO cohort in the first year of life. Three different clusters were identified: **Cluster 1** (in red) including subjects with weight trajectories more than 1 standard deviation above the cohort mean; **Cluster 2** (in green) with "normal" growth and **Cluster 3** (in blue) with a weight trajectory more than 0.5 standard deviations below the mean.

Table 3
Socio-demographic and delivery characteristics of the study sample by growth curves of the three clusters.

	CLUSTER 1 HIGHER CLASS	CLUSTER 2 NORMAL CLASS	CLUSTER 3 LOWER CLASS	p-value
N = 237 (100 %)	57(24.1 %)	83(35.0 %)	97(40.9 %)	
DEMOGRAPHIC CHARACTERISTICS				
	N(%)	N(%)	N(%)	
NPCS[#]:				**0.050**
PRIOLO	19 (33.3 %)	48 (57.8 %)	50 (51.5 %)	
CROTONE	27 (47.4 %)	22 (26.5 %)	29 (29.9 %)	
MILAZZO	11 (19.3 %)	13 (15.7 %)	18 (18.6 %)	
PARENT CHARACTERISTICS				
	N(%)	N(%)	N(%)	
Marital status[#]:				0.593
Married	39 (68.4 %)	50 (61.0 %)	65 (67.0 %)	
Unmarried	18 (31.6 %)	32 (39.0 %)	32 (33.0 %)	
Educational level[#]:				0.311
High	18 (32.1 %)	30 (36.1 %)	28 (28.9 %)	
Medium	30 (53.6 %)	39 (47.0 %)	60 (61.9 %)	
Low	8 (14.3 %)	14 (16.9 %)	9 (9.28 %)	
Type of Delivery[#]:				**0.034**
Caesarean	7 (12.3 %)	26 (31.3 %)	25 (25.8 %)	
Vaginal	50 (87.7 %)	57 (68.7 %)	72 (74.2 %)	
Maternal folic acid supplementation[#]:				0.310
No	7 (12.3 %)	14 (16.9 %)	9 (9.28 %)	
Yes	50 (87.7 %)	69 (83.1 %)	88 (90.7 %)	
Previous pregnancy[#]:				0.066
Nulliparous	24 (42.1 %)	38 (46.9 %)	57 (60.0 %)	
Parous	33 (57.9 %)	43 (53.1 %)	38 (40.0 %)	
Smoking during pregnancy[#]:				0.095
No	56 (98.2 %)	73 (89.0 %)	87 (89.7 %)	
Yes	1 (1.8 %)	9 (11.0 %)	10 (10.3 %)	
Alcohol consumption during pregnancy[#]:				0.140
No	57 (100 %)	76 (93.8 %)	92 (94.8 %)	
Yes	0 (0.00 %)	5 (6.2 %)	5 (5.2 %)	
	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	
Maternal age(years) ◆	30.0 [27.0;34.0]	31.0[28.0;34.0]	32.0 [29.0;35.0]	0.129
Maternal pre-pregnancy BMI (kg/m^2) ◆	23.5 [20.9;26.8]	22.4[20.0;24.8]	22.0 [19.7;24.0]	0.077
Maternal weight gain (kg) ◆	11.6 [8.57;15.0]	12.0[10.0;14.1]	11.1 [9.10;14.1]	0.677
Maternal pre-pregnacy weight(kg) ◆	64.0 [57.0;72.3]	60.0[55.5;66.8]	57.0 [52.8;65.0]	**0.005**
Paternal weight(kg) ◆	79.0 [71.0;85.5]	80.0[75.0;85.0]	75.0 [70.0;82.1]	0.069
Gestational age (weeks) ◆	40.0 [39.0;40.0]	39.0[38.5;40.0]	39.0 [38.0;40.0]	**0.035**
CHILD CHARACTERISTICS				
	N(%)	N(%)	N(%)	
Child sex[#]:				0.638
Female	21 (36.8 %)	36 (43.4 %)	43 (44.3 %)	
Male	36 (63.2 %)	47 (56.6 %)	54 (55.7 %)	
	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	
Child weight at delivery (g) ◆	3645 [3530;3850]	3400 [3195;3525]	3060 [2840;3280]	**<0.001**
Child length at delivery (cm) ◆	51.0 [50.0;52.0]	50.0[50.0;51.0]	50.0 [49.0;50.0]	**<0.001**
Child weight at 6 months (g) ◆	8800 [8575;9300]	7900 [7610;8400]	6900 [6388;7502]	**<0.001**
Child weight at 12 months (g) ◆	12,000 [10550;12625]	10,030 [10000;10550]	9000 [8600;10000]	**<0.001**

SD = standard deviation; [Q1-Q3] = [1st and 3rd quartile]; NPCS = National Priority Contaminated Site; BMI = Body Mass Index; [#] p values from Chi-squared test; ◆ p values from Kruskal-Wallis test.

0.84); lower vs normal: HCB OR = 2.85 (95 %CI: 1.46; 5.58)] but not in females' group [higher vs normal: HCB OR = 0.90 (95 %CI: 0.44; 1.84); lower vs normal: HCB OR = 1.81 (95 %CI: 0.77; 4.25)]. The interaction analysis confirmed that sex was a mediator of the association between HCB and growth trajectories. Indeed, the interaction term suggests that HCB showed a greater effect in reducing infant growth in males than in females [higher vs normal: p-value < 0.001; lower vs normal: p-value < 0.01].

A statistically significant increased risk of belonging to the "Higher" class was observed in females for both PCB-153 [higher vs normal: PCB-153 OR = 2.29 (95 %CI: 1.11; 4.72)] and PCB-180 [higher vs normal: PCB-180 OR = 3.57 (95 %CI: 1.60; 7,97)]. No statistically significant associations were identified for males (PCB-153 [higher vs normal: OR = 0.97 (95 %CI: 0.49;1.93)], PCB-180 [higher vs normal: OR = 1.07 (95 % CI: 0.53;2.14)]). The result was confirmed by a positive association between the "Higher" class and the PCB sum in females [higher vs normal: $\sum PCB_{(138,153,180)}$ OR = 2.23 (95 %CI: 1.09; 4.55)], but not in males [higher vs normal: $\sum PCB_{(138,153,180)}$ OR = 0.93 (95 %CI: 0.46; 1.88)]. The interaction term between exposure to all the PCB congeners (PCB-138, PCB153 and PCB-180) and sex was statistically significant and revealed a greater effect of PCB exposure on excessive growth in females compared to males (higher vs normal: p-value < 0.001 for all PCBs and $\sum PCB_{(138,153,180)}$). Conversely, cord Se concentrations were associated with a reduced risk of belonging to the "Higher" class in the total sample [higher vs normal: Se OR = 0.60 (95 %CI: 0.38; 0.95)] and in males [higher vs normal: Se OR = 0.48 (95 %CI: 0.26; 0.90)]. No statistically significant results were identified in females subgroup [higher vs normal: Se OR = 0.66 (95 %CI: 0.31; 1.39)]. The interaction

Table 4
Concentration of trace elements and Persistent Organic Pollutants in cord serum reported as median and interquartile range for each cluster of growth curves. The $\sum PCB_{(138,153,180)}$ was generated by summing PCB-138, PCB-153 and PCB-180.

	CLUSTER 1 HIGHER CLASS	CLUSTER 2 NORMAL CLASS	CLUSTER 3 LOWER CLASS	p-value◆
N = 237 (100 %)	57(24.1 %)	83(35.0 %)	97(40.9 %)	
CORD CHEMICALS	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	MEDIAN[Q1-Q3]	
Se (μg/L)	52.0 [47.0–58.0]	53.0 [48.0–58.5]	51.0 [46.0–58.0]	0.623
Zn (μg/L)	877 [784–950]	881 [761–961]	849 [791–950]	0.781
Cu (μg/L)	377 [303–485]	378 [308–486]	400 [321–485]	0.611
HCB (ng/L)	12.9 [10.3–17.8]	20.2 [11.8–24.5]	16.8 [12.9–24.6]	**0.004**
p'p'-DDE (ng/L)	92.0 [56.1–147]	92.6 [55.4–150]	99.7 [60.5–163]	0.821
PCB-138 (ng/L)	11.7 [7.70–17.8]	10.3 [7.93–19.6]	13.0 [9.89–22.7]	0.181
PCB-153 (ng/L)	18.1 [12.1–29.2]	19.5 [12.4–35.5]	23.6 [14.7–34.8]	0.163
PCB-180 (ng/L)	11.5 [6.21–20.0]	11.3 [6.73–22.4]	13.9 [8.65–24.6]	0.107
$\sum PCB_{(138,153,180)}$ (ng/L)	39.6 [27.0;66.2]	42.2 [28.3;78.7]	51.0 [32.7;76.9]	0.143

[Q1-Q3] = [1st and 3rd quartile]; ◆ p values from Kruskal-Wallis test.

analysis showed that sex modified the relationship between Se levels and growth trajectories. Reduction of excessive growth by Se was more pronounced in males than females [higher vs normal: p-value < 0.01].

Since the number of confounders was relatively high, we conducted an optimized multinomial regression with stepwise confounder selection (Model 2). Consequently, the explanatory variables were selected for each chemical. The results shown in Fig. 4 confirm the results observed for Model 1, while Fig. S6 shows the results of the interaction analysis. In brief, exposure to higher HCB concentrations increased the risk of lower growth during the first year of life in the total study sample [higher vs normal: HCB OR = 0.53(95 %CI:0.34;0.83); lower vs normal: HCB OR = 1.67 (95 % CI:1.10;2.54)]. The results are consistent in males [higher vs normal: HCB OR = 0.32(95 % CI:0.16;0.61); lower vs normal: HCB OR = 2.03 (95 % CI:1.13;3.64)], but not statistically significant in females [higher vs normal: HCB OR = 0.80 (95 % CI:0.42;1.55); lower vs normal: HCB OR = 1.22 (95 % CI:0.56;2.36)]. The interaction term also confirmed the stronger negative effect of HCB exposure on growth in males than in females (p value < 0.001 for both higher vs normal and lower vs normal comparisons).

PCB-180 levels showed a significant positive association with the "Higher" class in females [higher vs normal: PCB-180 OR = 3.87 (95 % CI:1.68;8.93)]. Conversely, the association was not statistically significant for males [higher vs normal: PCB-180 OR = 0.90 (95 % CI:0.48;1.70)]. Accordingly, the interaction analysis confirmed that sex moderated the relationship between PCB-180 and growth during the first year of life. Indeed, females exposed to PCB-180 were more likely to fall into the "Higher" growth category (higher vs normal: p-value < 0.001).

Thus, Model 2 confirmed the results for Se obtained in Model 1. A lower probability of belonging to the "Higher" class was confirmed for Se in the total group [higher vs normal: Se OR = 0.60(95 % CI: 0.38;0.95)]. No statistically significant effect of sex on associations between Se and growth trajectories was identified.

Given the high correlation between PCBs and HCB (Fig. S7), we performed a multinomial ridge penalty regression (Model 3) for each comparison (Fig. 5) to prevent overfitting and address multicollinearity.

As reported for Model 1 and Model 2, the cord HCB trend was confirmed in Model 3 for both the total population [higher vs normal: HCB OR = 0.45 (95 % CI: 0.23; 0.90); lowers vs normal: HCB OR = 1.97 (95 % CI:1.07;3.65)] and males [higher vs normal: HCB OR = 0.33 (95 % CI:0.12;0.87); lower vs normal: HCB OR = 2.17 (95 % CI:0.94;5.00)]. Exposure to Se increased the probability of belonging to the "Normal" class in the overall analysis [higher vs normal: Se OR = 0.50 (95 % CI: 0.26;0.97)]. Model 3 validated the association between PCB-180 levels and the "Higher" class in females [higher vs normal: PCB-180 OR = 24.10(95 % CI:1.33;438.24)].

Furthermore, we investigated the relationship between *in utero* exposure to chemical mixtures and growth trajectories using the BKMR model. First, we examined hierarchical variable selection PIPs for growth trajectories (Table 5). In the "Higher" group, OCs showed the highest group-PIPs, with a value of 0.63, followed by PCBs, with a group importance very close to the threshold (0.49). Similar results were identified for the "Lower" cluster, showing group-PIPs equal to 0.61 and 0.42 for OCs and PCBs, respectively. HCB had the greatest importance in both the "Higher" and "Lower" groups, showing conditional-PIPs of 0.87 and 0.75, respectively. Among PCBs, PCB-180 had the highest conditional-PIP value: 0.49 for the "Higher" group and 0.35 for "Lower." No significant difference was observed for EEs. These results suggest that the association between this mixture and growth trajectories was primarily driven by HCB.

Univariate exposure–response function was visually examined to identify non-linear relationships for each exposure with the growth trajectories while fixing all other exposures to their 50th percentile. The results obtained for Se, HCB, and PCB-180 (Fig. 6) confirmed the data obtained in the regression models. Increasing levels of Se and HCB were associated with a higher probability of belonging to the "Normal" than "Higher" group. In addition, HCB showed a positive exposure–response function with the "Lower" class. In contrast, PCB-180 exposure increased the probability of belonging to the "Higher" group. All the exposure–response functions appeared linear, except for HCB in the "Higher versus Normal" comparison. Detailed results are shown in Figs. S8 and S9. Due to the reduced sample size resulting from splitting the dataset to conduct separate analyses ("Lower" and "Higher" groups), the credible intervals (shaded gray areas) are consistently wide across all exposures. This may have limited the precision of the exposure–response estimates, making the detection of significant associations more challenging.

As reported in Fig. S10, we examined the overall effect of the environmental mixture (95 %CI) for the two comparative groups – Higher (panel A) and Lower (panel B) – relative to the "Normal" reference group. The effect of the mixture is defined as the difference in the response when all exposures are fixed at a specific quantile (in the range 0.25——0.75) compared to the condition where all exposures are fixed at their median value. No statistically significant evidence of mixture effect was identified.

Finally, we examined bivariate exposure–response functions for each pollutant, while fixing the second exposure at various percentiles (25th, 50th and 75th) and the remaining exposures at their median values. The results revealed that the slope of the exposure–response function for one pollutant remained similar across different quantiles of exposure to other chemicals, suggesting that no interaction effects were present (Figs. S11 and S12). Fig. 7 reports the exposure–response curves for HCB and PCB-180 in relation to Se levels, stratified by different exposure quantiles. Fig. 7A and 7B show the results for the "Higher" group and "Lower" groups, respectively, using the "Normal" group as reference.

4. Discussion

The present study examined the potential influence of intrauterine toxicant exposures on infant growth during the first year of life in a sample of 237 mother-infant pairs participating in the NEHO residential birth cohort. We investigated the impact of cord pollutants using growth curve trajectories to understand how fetal exposures affect postnatal growth. Our major findings regarding the first year of life were: i)

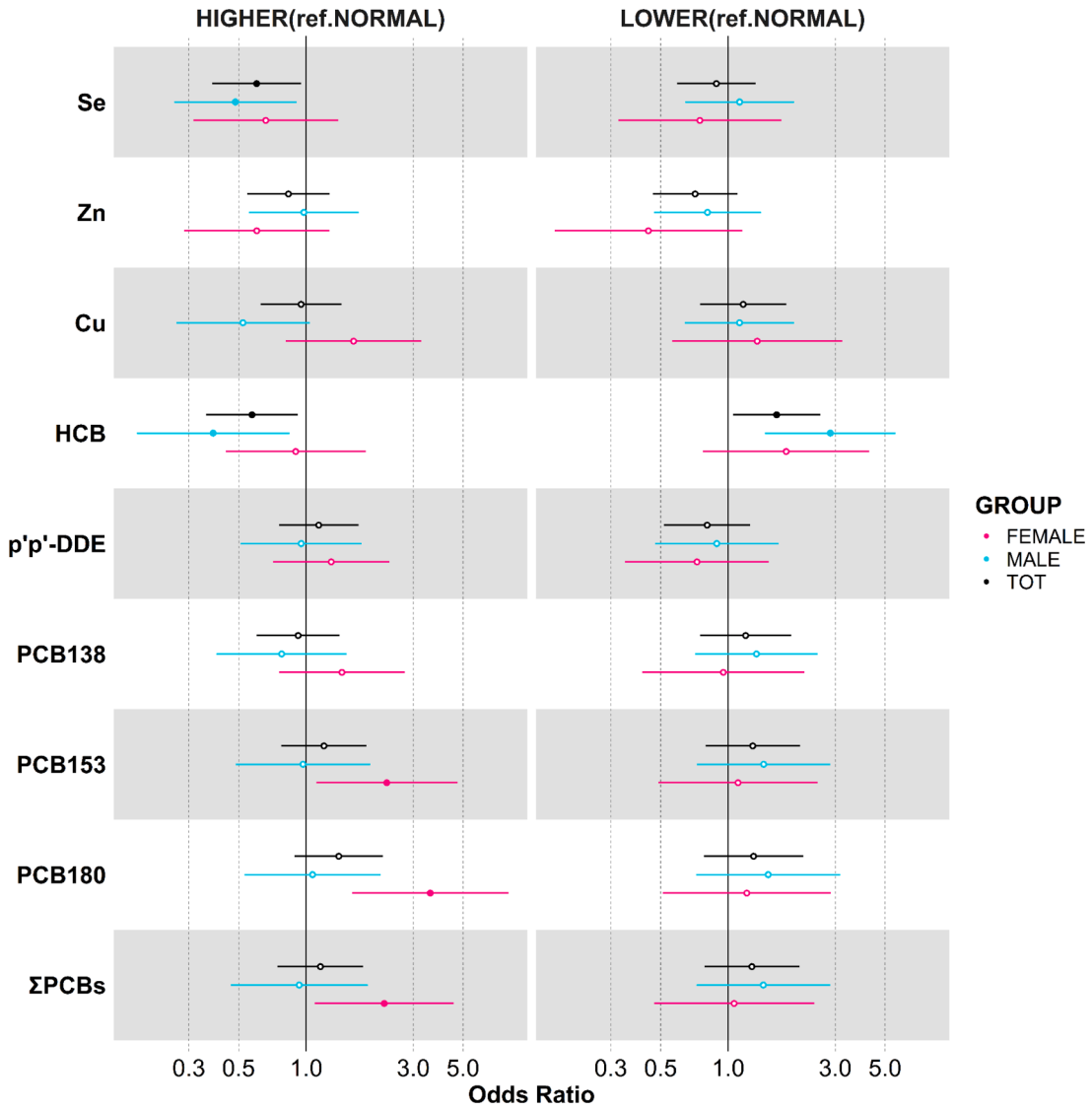

Fig. 3. Model 1 results. Associations (ORs and 95%CIs) between concentrations of single cord analytes and growth trajectories obtained using the multinomial regression models correcting for all confounders (Model 1).

increased *in-utero* exposure to HCB was associated with a reduction of infant growth, particularly among males; ii) PCB-180 was associated with an increased risk of elevated body weight in female infants; iii) Se was associated with a reduction of the risk of excessive growth.

Within our cohort, increased HCB levels were associated with a higher risk of lower growth in the first year of life. This effect was consistent for the total population across various comparisons, including between "Higher" versus "Normal" growth and "Lower" versus "Normal" growth in all the models considered. HCB's influence was partly confirmed in Model 3 (the ridge penalty regression model) for the male subgroup, showing statistically significant associations at the 10 % level with the "Lower" class. Although this association was only close to the level of significance in Model 3, the interaction term estimates from Models 1 and 2, along with the sex-stratified analyses, indicated that the association between HCB exposure and reduced growth was more pronounced in male infants. Data on intrauterine exposure to HCB and its effects on growth during childhood are controversial. Some studies suggest a potential association between intrauterine HCB exposure and increased obesity and overweight risk during early infancy (Smink et al., 2008; Agay-Shay et al., 2015; Stratakis et al., 2022), along with a broader effect of HCB on early childhood cardiometabolic risk (Güil-Oumrait et al., 2021). In contrast, studies conducted on low exposure cohorts report null association between prenatal HCB exposure and growth parameters at 3 and 7–9 years (Verhulst et al., 2009; Delvaux et al., 2014). Furthermore, a 2014 study found that elevated levels of *in-utero* HCB exposure were associated with accelerated weight gain within the first six months of life. Moreover, at 14 months, the same group of children showed an elevated rate of being overweight (Valvi et al., 2014). Interestingly, the group of fast-growing subjects had a lower birth weight compared to the average slow-growing group. Since our observations of the association between HCB exposure and growth curves referred to the first year of life, this may reflect an initial negative impact of HCB on intrauterine development. Other studies reported negative effects of HCB on birth weight (Lopez-Espinosa et al., 2011) and on intrauterine linear growth (Ribas-Fitó et al., 2002). Subsequently, when rapid growth occurs, compensatory effects may emerge, possibly increasing the risk of obesity. Residual confounding factors may contribute to these inconsistent findings as unmeasured factors, such as genetics, postnatal diet, and other environmental exposures, could affect both growth trajectories and susceptibility to HCB. Moreover, the cord levels of HCB found in our cohort were lower than those reported in the above-mentioned studies: this could partially explain the differences in the observed associations.

Furthermore, the graphical analysis of the univariate

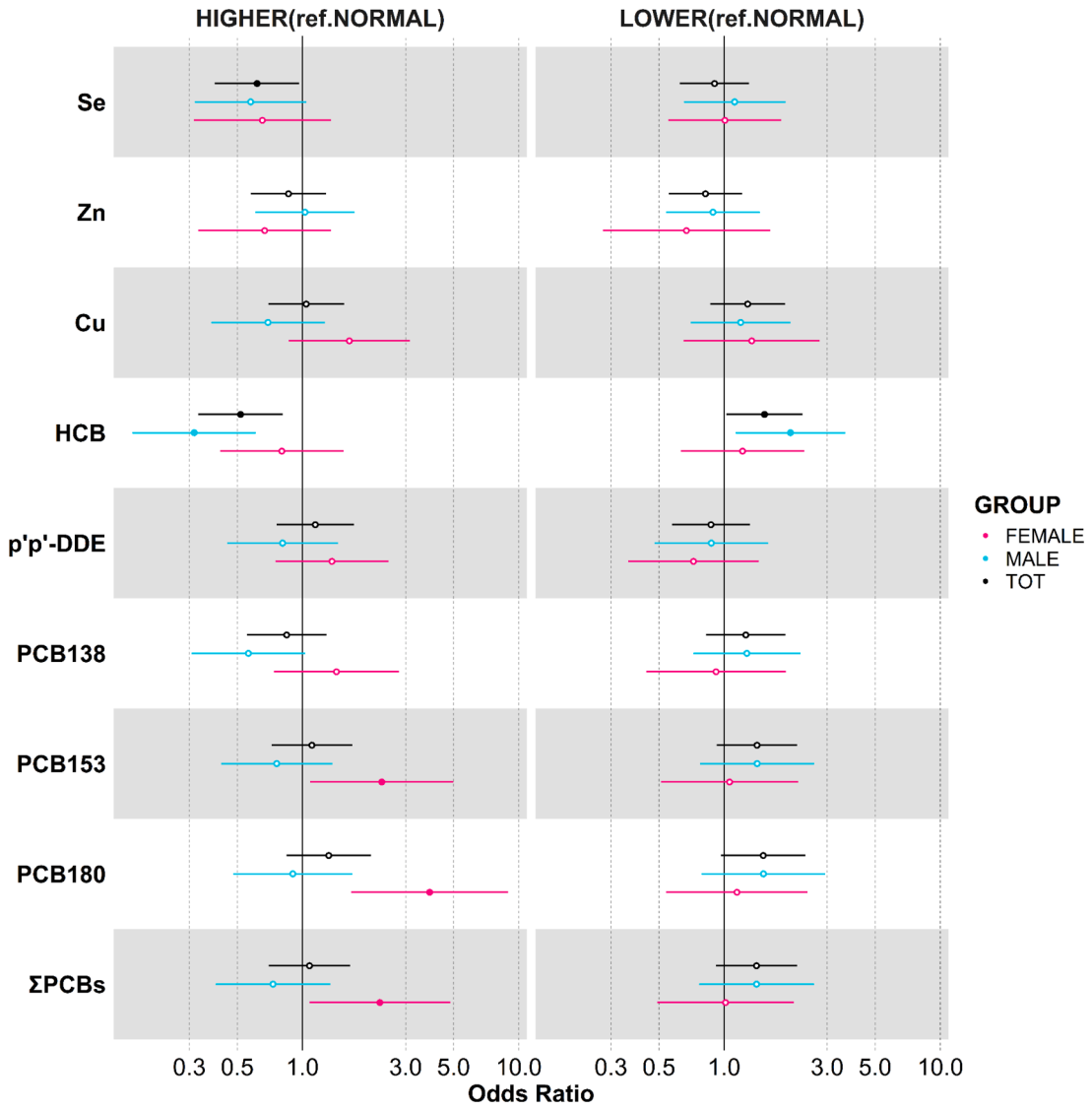

Fig. 4. Model 2 results. Associations (ORs and 95%CIs) between concentrations of single cord chemicals and growth trajectories obtained using the multinomial regression models selecting confounders by stepwise procedure (Model 2).

exposure–response functions suggests a non-linear association between HCB and reduced growth in the "Higher" versus "Normal" comparisons. A similar non-linear relationship was found by Güil-Oumrait and colleagues between HCB levels and BMI Z-score (Güil-Oumrait et al., 2021). Nevertheless, the association between increased HCB concentration and reduced growth in our sample seems quite robust and was confirmed by the three different regression models. Additionally, when mixture effects were tested by means of BKMR models, HCB was the major factor contributing to the association between exposures and growth curves, underscoring the importance of HCB exposure in our study population.

In terms of sex differences in the association between HCB exposure and growth reduction, our findings support a more pronounced negative association in male infants. However, none of the referenced studies identified a similar effect in relation to the health outcomes examined through stratified or interaction analysis.

Within our sample, we observed a significant positive association between elevated growth during the first year of life and cord serum concentrations of PCB-180 in the female subgroup. This finding was consistent with the results of Model 1 and Model 2, which incorporated interaction terms between sex and PCB-180. The interaction estimates suggest that the association between PCB-180 exposure and excessive growth is stronger in females than males. Though the levels of cord PCBs in our study population were relatively low compared to other cohort studies (Sala et al., 2001; Govarts et al., 2011; Lopez-Espinosa et al., 2011; Lopes et al., 2014; Junqué et al., 2020), our results are consistent with those reported by Tang-Peronard suggesting an exposure level-dependent effect of PCBs on growth trajectories and/or obesity risk (Tang-Péronard et al., 2014). In particular, the latter study hypothesized that, at low concentrations such as ours, the obesogenic effect of PCBs is observed only in females. Conversely, at higher PCB concentrations, toxic effects, including the induction of inflammation and oxidative stress, become prominent. Accordingly, Hertz-Picciotto and colleagues identified a sex-specific impact of prenatal PCB exposure on early-life growth. They found that increased PCB concentrations during pregnancy were associated with reduced birth weight in males and increased growth rates in females up to the age of five (Hertz-Picciotto et al., 2005). Moreover, Montazeri and colleagues identified an association between prenatal PCB exposure and a growth pattern characterized by low birth weight followed by accelerated BMI trajectories (Montazeri et al., 2023). A sensitivity analysis stratified by sex did not reveal any evidence of a female-specific association for PCBs.

Finally, BKMR results indicated a moderate contribution of PCBs in the multipollutant analysis. However, these findings may be influenced by the sex-dependent association between PCBs and growth curves that

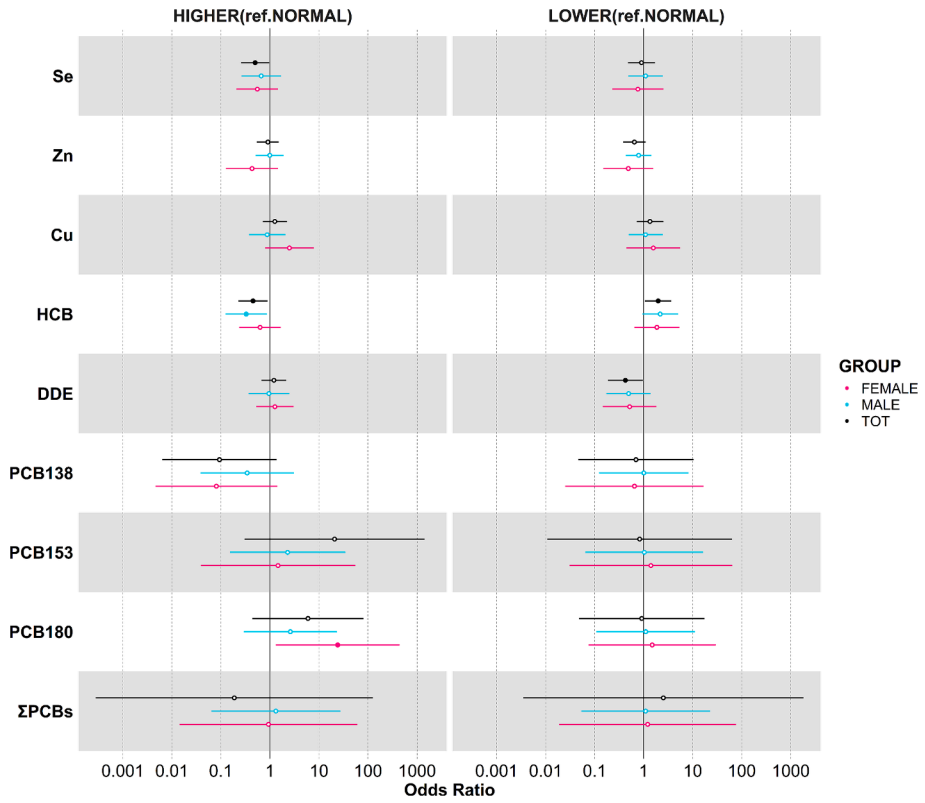

Fig. 5. Model 3 results. Multinomial ridge penalty regression results (ORs and 95 %CIs) between cord analytes and growth trajectories correcting for all confounders (Model 3). The values in the x axis are presented on a logarithmic scale to reduce the range of values and enhance the clarity of the data distribution.

Table 5
BKMR hierarchical variable selection estimates for environmental multichemical exposures and growth trajectories. Both group- and conditional- Posterior Inclusion Probabilities are reported for the "Higher" and "Lower" trajectories (reference "Normal").

Group	Exposures	Higher(ref. Normal)		Lower(ref. Normal	
		Group-PIP	Conditional-PIP	Group-PIP	Conditional-PIP
EEs		0.28		0.33	
	Se		0.39		0.35
	Zn		0.37		0.32
	Cu		0.24		0.34
OCs		0.63*		0.61*	
	HCB		0.87*		0.75*
	p,p'-DDE		0.13		0.25
PCBs		0.49		0.42	
	PCB-138		0.16		0.37
	PCB-153		0.36		0.28
	PCB-180		0.49		0.35

*A threshold of 0.5 was used to identify the relative importance of group or individual exposures.

emerged in our sample.

In terms of EEs, higher Se cord levels were associated with a reduced risk of excessive growth in the first year of life. The effects appear to be predominantly linked to males, although this was demonstrated only in Model 1 when sex was included as an interaction term. Biological differences between the sexes, such as hormonal regulation and metabolism, may modulate the effects of EEs on growth (Xiao et al., 2022). However, the limited sample size and variability in exposure levels may have limited the statistical power to detect consistent sex-specific effects. Despite these inconsistencies, interest in EEs remains high, as several studies have investigated the potential adverse effects of both deficiencies and excessive levels of EEs in maternal blood on pregnancy outcomes (Gernand et al., 2016; Zoroddu et al., 2019; Grzeszczak, Kwiatkowski and Kosik-Bogacka, 2020; Dahlen, Reynolds and Caton, 2022; Gohari et al., 2023). A recent *meta*-analysis of 50 studies found significant associations between low cord levels of Se and low birth weight (Atazadegan et al., 2022). In addition, Se deficiency was associated with obesity and central adiposity in school children (Ortega et al., 2012). Se levels are closely related to maternal nutritional status and can be affected by geographical and cultural dietary patterns (Izquierdo Alvarez et al., 2007; Liu et al., 2017; Watson et al., 2020), making it difficult to establish reference values. Moreover, mother to fetus transfer of these elements via the placenta, crucial for fetal development, can be influenced by genetic factors and exposure to harmful substances. Under these conditions, fetal element levels may not be solely regulated by maternal concentrations (Bermúdez et al., 2015). To explore potential interaction effects between EEs and environmental pollutants, we employed BKMR analysis to evaluate whether EEs might mitigate adverse effects of HCB or PCB-180 on child growth. However, no significant interactions were identified, possibly due to the limited sample size and the further subdivision of the dataset required for the analysis. Nevertheless, given the involvement of Se in defense against oxidative stress (Michiels et al., 1994), lipid metabolism (Steinbrenner, 2013) and thyroid functions (Jain, 2014), the role of EEs in shaping growth trajectories and modulating the effects of ECDs must be further explored.

Since no significant difference in the socio-demographic characteristics and lifestyles was found between the study sample and the entire NEHO cohort, we believe that the study findings can be extended to the whole cohort.

Overall, our results highlight an effect of HCB and PCB exposure on growth during the first year of life. The significance of this study lies particularly in the fact that we investigated concentrations at relatively low exposure range. These two POPs are often reported as highly correlated in biomonitoring studies, and their interference with

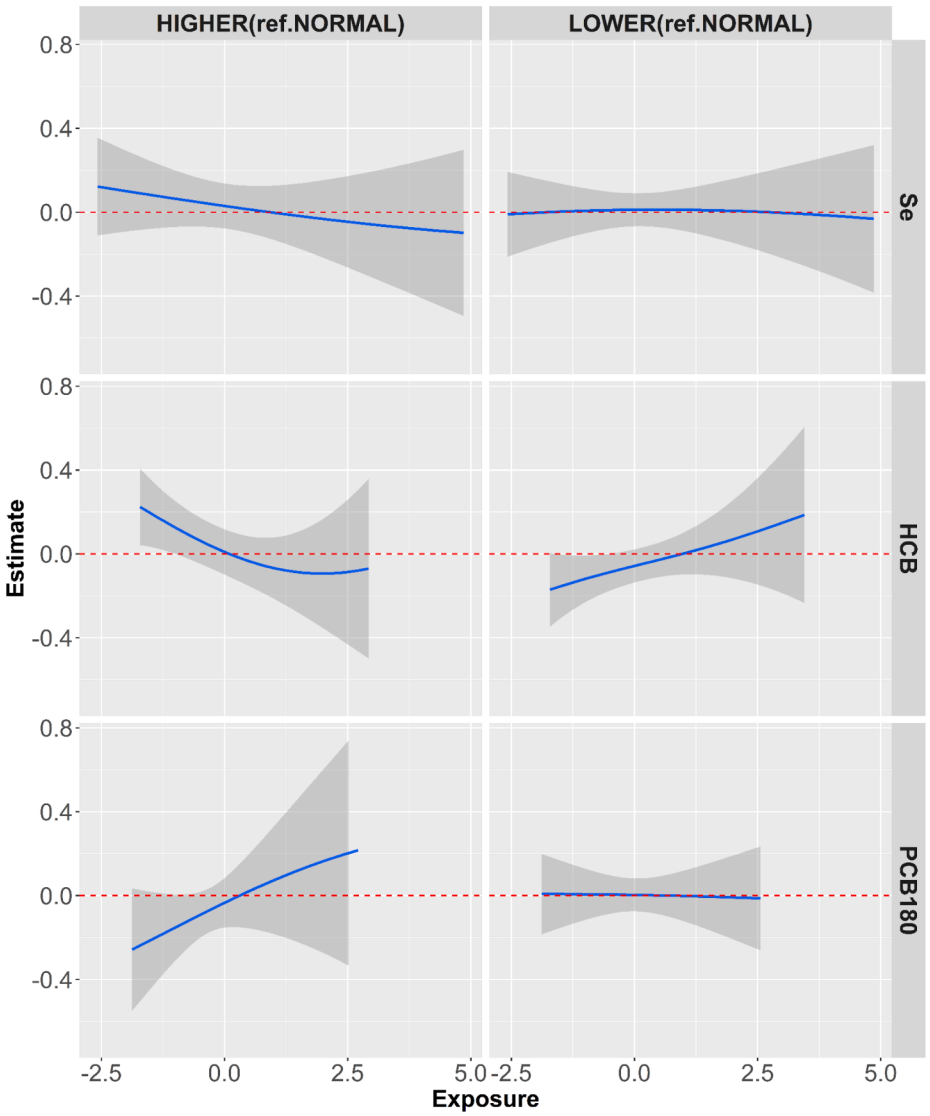

Fig. 6. BKMR estimated associations between Se, HCB and PCB-180 exposure levels and growth trajectories. Univariate exposure–response functions are shown for Se, HCB, and PCB180. "Higher" group associations are on the left, while the "Lower" group associations are on the right, with both referenced to the "Normal" group. Blue lines represent estimated effects; shaded gray areas denote the 95% credible intervals. Red dashed horizontal lines at zero indicate no association.

hormonal regulation has been confirmed. Despite this, in our study population, they appear to shape growth trajectories differently. The different effects of *in-utero* HCB and PCB exposure we observed may be explained by the specific hormonal pathways altered by these endocrine disruptors. PCBs have been shown to disrupt the hypothalamic-pituitary–gonadal axis (Weis et al., 2023). In contrast, HCB primarily interferes with thyroid hormone signaling, which plays a critical role in metabolic processes and growth (Mughal, Fini and Demeneix, 2018). Interestingly, EEs and, in particular, Se, Cu, and Zn are essential for thyroid function and hormone metabolism (Rasic-Milutinovic et al., 2017). Although our data did not demonstrate any protective role of EEs against exposure to EDCs, this aspect warrants further investigation, especially in the context of primary prevention. Similarly, the observed sex-specific associations between EDC exposure and growth trajectories emphasize the importance of incorporating sex-specific analyses in studies examining the effects of EDCs on health outcomes. This is crucial for implementing effective and specific primary and secondary prevention measures.

5. Strengths and limitations

A key strength of this study is the inclusion of EEs alongside EDCs such as OC pesticides and PCBs. Notably, the assessment of EE levels on the fetal side is underrepresented in the literature, highlighting the novelty and significance of our approach.

Another major strength is the monthly follow-up of weight measurements across the first year of life. Weight values, measured by a pediatrician and self-reported by mothers, provide detailed data for constructing growth trajectories.

However, the main limitation of our study was its entirely voluntary recruitment which may have introduced bias due to socio-cultural background of the participants. Although we corrected the models for a wide range of covariates, unmeasured or uncontrolled variables (such as environmental influences or lifestyles) which can affect outcomes may not be fully controlled. Among these, infant diet could influence growth trajectories, even though the feeding variability between subjects of this age is limited. Additionally, despite the thorough follow-up for weight measurements, some data points were missing, necessitating a threshold of at least two measurements per child for inclusion in the

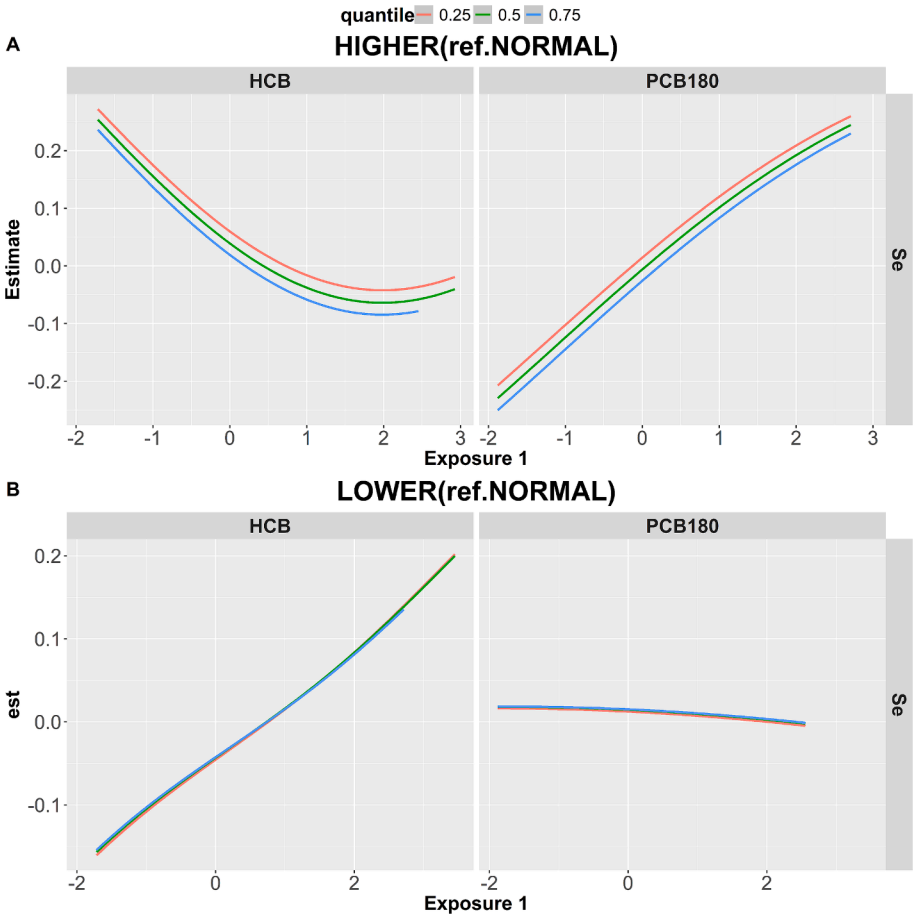

Fig. 7. Bivariate exposure–response functions from BKMR analysis for the "Higher" (A) and "Lower" (B) groups. Each cell reports the exposure–response of the column indicator (HCB or PCB-180) with the row indicator (Se) fixed at the 25th, 50th, and 75th percentile. The remaining indicators were fixed at their medians.

growth trajectory analysis. Nevertheless, we included a sufficient number of participants, allowing for the identification of distinct growth patterns.

Furthermore, GBMT was employed to distinguish three different growth weight trajectories in our population. This method offers an easy interpretation of the results and can handle missing data by fitting the model using maximum likelihood estimation assuming the data are missing at random.

Although using cohort-specific measurements instead of WHO child standards may limit direct comparisons with other studies, it provides more accurate reflections of growth patterns, especially in different populations. As reported in two different UK cohorts (Wright et al., 2008), the usage of WHO standards is not representative of birth weight and can misclassify underweight infants. Similar findings were reported for Asian (Natale and Rajagopalan, 2014), Indian (Khadilkar, Khadilkar and Chiplonkar, 2010), and European cohorts (Christesen et al., 2016). Thus, the adoption of reference values specific for the NEHO cohort enhances the relevance of our findings to our cohort while offering a comparative analysis with WHO standards.

The wide confidence interval for the association between PCB-180 exposure and higher growth in females indicates low precision, likely due to the small sample size and data variability. Lastly, by adapting the BKMR model for multinomial outcomes through separate binary comparisons, the resulting reduced sample size led to wider credible intervals across exposures. This may impact the overall mixture effects, where no statistically significant results were obtained. This is also likely due to the different influences of individual pollutants within the mixture on growth, with some pollutants exerting opposing effects (such as HCB and PCB-180). This aspect may limit the precision of the exposure–response estimates, making it more challenging to detect results consistent with previous regression models.

CRediT authorship contribution statement

Ilaria Cosentini: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Silvia Ruggieri:** Writing – review & editing, Supervision, Investigation. **Paolo Colombo:** Writing – review & editing, Methodology. **Fabrizio Bianchi:** Writing – review & editing, Supervision, Resources. **Liliana Cori:** Writing – review & editing, Supervision. **Melania Casella:** Writing – review & editing, Data curation. **Elisa Eleonora Tavormina:** Writing – review & editing, Methodology. **Fabio Cibella:** Supervision, Resources, Project administration, Investigation, Funding acquisition. **Gaspare Drago:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation.

Funding

This research was funded by the "Progetto Obiettivo Piano Sanitario Nazionale 2019 – Linea 4 – Piano Nazionale Prevenzione della Regione Siciliana (Italy)".

The NEHO cohort was supported by the International Centre of advanced Study in Environment, Ecosystem and Human Health (CISAS), a multidisciplinary project on environment/health relationships funded by the Italian Ministry of Education, Universities and Research (MIUR) and approved by the Interministerial Committee for Economic Planning (CIPE) – a body of the Italian Government –with Resolution no. 105/2015 of December 23, 2015.

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.

Acknowledgments

We wish to thank our colleagues involved in the Piccolipiù birth cohort for their support in defining questionnaires and the structure of the study. This work was conducted as part of a scientific collaboration among the National Research Council of Italy—Institute for Biomedical Research and Innovation, Palermo, the Department of Epidemiology, Lazio—Regional Health System, Rome, and the Epidemiology Unit of the Anna Meyer Children's University Hospital, Florence. We extend our thanks for the essential support provided by the doctors and nurses at the "Umberto I" Hospital in Syracuse, the General Hospital of Lentini, the "G. Fogliani" Hospital in Milazzo and the "San Giovanni di Dio" Hospital in Crotone where the pregnant women were enrolled. We also express our appreciation for the technical assistance provided by Mr. Alessandro Pensato and Dr. Gaetano Spinelli.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109225.

Data availability

Data will be made available on request.

References

Adair, L.S. *et al.* (2013) 'Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies', *Lancet*, 382(9891). Available at: https://doi.org/10.1016/S0140-6736(13)60103-8.

Agay-Shay, K. *et al.* (2015) 'Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach', *Environmental health perspectives* [Preprint]. Available at: https://doi.org/10.1289/ehp.1409049.

Akaike, H., 1974. A new look at the statistical model identification. IEEE Trans. Autom. Control 19 (6), 716–723. https://doi.org/10.1109/TAC.1974.1100705.

Al-Kunani, A.S. et al. (2001) 'The selenium status of women with a history of recurrent miscarriage', BJOG: an international journal of obstetrics and gynaecology, 108(10), pp. 1094–1097.

Amir, S. et al. (2021) 'Endocrine Disruptors Acting on Estrogen and Androgen Pathways Cause Reproductive Disorders through Multiple Mechanisms: A Review', International journal of environmental research and public health, 18(4). Available at: https://doi.org/10.3390/ijerph18041464.

Atazadegan, M.A., et al., 2022. Association of selenium, zinc and copper concentrations during pregnancy with birth weight: a systematic review and meta-analysis. J. Trace Elem. Med. Biol.: Organ of the Society for Minerals and Trace Elements 69, 126903.

Bermúdez, L., et al., 2015. Assessment of ten trace elements in umbilical cord blood and maternal blood: association with birth weight. J. Transl. Med. 13, 291.

Bobb, J.F., et al., 2018. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ. Health: a Global Access Science Source 17 (1), 1–10.

Bobb, J.F. et al. (2015) 'Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures', Biostatistics , 16(3). Available at: https://doi.org/10.1093/biostatistics/kxu058.

Bonefeld-Jørgensen, E.C., et al., 2014. Biomonitoring and hormone-disrupting effect biomarkers of persistent organic pollutants in vitro and ex vivo. Basic Clin. Paharmacol. Toxicol. 115 (1), 118–128.

Bozdogan, H., 1987. Model selection and Akaike's Information Criterion (AIC): The general theory and its analytical extensions. Psychometrika 52 (3), 345–370.

Cai, A., Portengen, L., Govarts, E., Martin, L.R., Schoeters, G., Legler, J., Vermeulen, R., Lenters, V., Remy, S., 2023. Prenatal exposure to persistent organic pollutants and changes in infant growth and childhood growth trajectories. Chemosphere 314, 137695. https://doi.org/10.1016/j.chemosphere.2022.137695.

Cauzzo, C. et al. (2023) 'Birth size, growth trajectory and later cardio-metabolic risk', Frontiers in endocrinology, 14. Available at: https://doi.org/10.3389/fendo.2023.1187261.

Cho, J., Holditch-Davis, D., Miles, M.S., 2010. Effects of Gender on the Health and Development of Medically At-Risk Infants. J Obstet Gynecol Neonatal Nurs 39 (5), 536–549.

Christesen, H.T. et al. (2016) 'Short Stature: Comparison of WHO and National Growth Standards/References for Height', PloS one, 11(6). Available at: https://doi.org/10.1371/journal.pone.0157277.

Dahlen, C.R., Reynolds, L.P., Caton, J.S., 2022. Selenium supplementation and pregnancy outcomes. Front. Nutr. 9, 1011850.

Delvaux, I., et al., 2014. Prenatal exposure to environmental contaminants and body composition at age 7–9 years. Environ. Res. 132, 24–32.

Drago, G., et al., 2023. Exposure profiles in pregnant women from a birth cohort in a highly contaminated area of southern Italy. Sci. Rep. 13 (1), 1–12.

Duntas, L.H., 2020. Selenium and at-risk pregnancy: challenges and controversies. Thyroid Res. 13, 16.

Friedman, J.H., Hastie, T., Tibshirani, R., 2010. Regularization Paths for Generalized Linear Models via Coordinate Descent. J. Stat. Softw. 33, 1–22.

Garced, S., Torres-Sánchez, L., Cebrián, M.E., Claudio, L., López-Carrillo, L., 2012 Feb. Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and child growth during the first year of life. Environ Res. 113, 58–62. https://doi.org/10.1016/j.envres.2011.12.002.

GBD 2019 Risk Factors Collaborators, 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 1223–1249.

Gernand, A.D., et al., 2016. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nat. Rev. Endocrinol. 12 (5), 274–289.

Gohari, H., et al., 2023. Copper and zinc deficiency to the risk of preterm labor in pregnant women: a case-control study. BMC Pregnancy Childbirth 23 (1), 366.

Govarts, E. et al. (2011) 'Birth Weight and Prenatal Exposure to Polychlorinated Biphenyls (PCBs) and Dichlorodiphenyldichloroethylene (DDE): A Meta-analysis within 12 European Birth Cohorts', Environmental health perspectives [Preprint]. Available at: https://doi.org/10.1289/ehp.1103767.

Grzeszczak, K., Kwiatkowski, S., Kosik-Bogacka, D., 2020. The Role of Fe, Zn, and Cu in Pregnancy. Biomolecules 10 (8), 1176.

Güil-Oumrait, N., et al., 2021. Prenatal exposure to persistent organic pollutants and markers of obesity and cardiometabolic risk in Spanish adolescents. Environ. Int. 151, 106469.

Hertz-Picciotto, I., et al., 2005. In Utero Polychlorinated Biphenyl Exposures in Relation to Fetal and Early Childhood Growth. Epidemiology 16 (5), 648.

Izquierdo Alvarez, S., et al., 2007. 'Updating of normal levels of copper, zinc and selenium in serum of pregnant women', Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace. Elements 21 (Suppl 1), 49–52.

Jain, R.B., 2014. Thyroid function and serum copper, selenium, and zinc in general U.S. population. Biol. Trace Elem. Res. 159 (1–3), 87–98.

Junqué, E., et al., 2020. Changes of organochlorine compound concentrations in maternal serum during pregnancy and comparison to serum cord blood composition. Environ. Res. 182, 108994.

Khadilkar, V.V., Khadilkar, A.V. and Chiplonkar, S.A. (2010) 'Growth performance of affluent Indian preschool children: a comparison with the new WHO growth standard', Indian pediatrics, 47(10). Available at: https://doi.org/10.1007/s13312-010-0147-6.

Krönke, A.A., et al., 2022. Persistent organic pollutants in pregnant women potentially affect child development and thyroid hormone status. Pediatr. Res. 91 (3), 690–698.

Kumar, J., et al., 2014. Influence of persistent organic pollutants on oxidative stress in population-based samples. Chemosphere 114, 303–309.

Lewandowska, M. et al. (2019) 'First Trimester Serum Copper or Zinc Levels, and Risk of Pregnancy-Induced Hypertension', Nutrients, 11(10). Available at: https://doi.org/10.3390/nu11102479.

Liu, X. et al. (2017) 'Reference Values of 14 Serum Trace Elements for Pregnant Chinese Women: A Cross-Sectional Study in the China Nutrition and Health Survey 2010-2012', Nutrients, 9(3). Available at: https://doi.org/10.3390/nu9030309.

Longo, V., et al., 2022. A multipollutant low-grade exposure regulates the expression of miR-30b, Let-7a and miR-223 in maternal sera: Evidence from the NEHO cohort. Sci. Total Environ. 844, 157051.

Lopes, B. et al. (2014) 'Polychlorinated biphenyls (PCBs) and p,p'-dichlorodiphenyldichloroethylene (DDE) concentrations in maternal and umbilical cord serum in a human cohort from South Portugal', Chemosphere, 114. Available at: https://doi.org/10.1016/j.chemosphere.2014.04.111.

Lopez-Espinosa, M.J. et al. (2011) 'Prenatal exposure to organochlorine compounds and birth size', Pediatrics, 128(1). Available at: https://doi.org/10.1542/peds.2010-1951.

Magrini, A., 2022. Assessment of agricultural sustainability in European Union countries: a group-based multivariate trajectory approach', AStA. Advances in Statistical Analysis. J. German Statist. Soc. 106 (4), 673–703.

Maisano, M., et al., 2016. PCB and OCP accumulation and evidence of hepatic alteration in the Atlantic bluefin tuna, T. thynnus, from the Mediterranean Sea. Mar. Environ. Res. 121, 40–48.

Mehta, R., Krupa, C., Ahmed, T., Hamer, D.H., Al, M.A., 2023. Associations between maternal and infant selenium status and child growth in a birth cohort from Dhaka. Bangladesh. Br J Nutr. 130 (9), 1558–1572. https://doi.org/10.1017/S0007114523000739.

Michiels, C., et al., 1994. Importance of Se-glutathione peroxidase, catalase, and Cu/Zn-SOD for cell survival against oxidative stress. Free Radic. Biol. Med. 17 (3), 235–248.

Montazeri, P., et al., 2023. 'Prenatal Exposure to Multiple Endocrine-Disrupting Chemicals and Childhood BMI Trajectories in the INMA Cohort Study', Environmental health perspectives, 131(10). Available at: https://doi.org/10.1289/EHP11103.

Moschonis, G., et al., 2023. Likelihood of obesity in early and late childhood based on growth trajectory during infancy. Int. J. Obes. (Lond) 47 (7), 651–658.

Mughal, B.B., Fini, J.-B., Demeneix, B.A., 2018. Thyroid-disrupting chemicals and brain development: an update. Endocr. Connect. 7 (4), R160.
Nagin, D.S., et al., 2018. Group-based multi-trajectory modeling. Stat. Methods Med. Res. 27 (7), 2015–2023.
Natale, V. and Rajagopalan, A. (2014) 'Worldwide variation in human growth and the World Health Organization growth standards: a systematic review', BMJ open, 4(1). Available at: https://doi.org/10.1136/bmjopen-2013-003735.
Oliveri, E., et al., 2022. Interferences between natural and anthropic hazards in marine-coastal environments: Assessing transport from land to the offshore systems in the Crotone basin (Ionian Sea). Estuar. Coast. Shelf Sci. 271, 107854.
Ortega, R.M., et al., 2012. 'Young children with excess of weight show an impaired selenium status', International journal for vitamin and nutrition research. Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung. Journal International De Vitaminologie et De Nutrition 82 (2), 121–129.
Oshiro, C.E.S. et al. (2022) 'First year infant weight trajectories predict overweight/obesity at age 2 in a diverse population', Obesity research & clinical practice, 16(5). Available at: https://doi.org/10.1016/j.orcp.2022.08.007.
R Core Team (2023) R Core Team (2023) R A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. Available at: https://www.R-project.org/ (Accessed: 3 July 2024).
Rasic-Milutinovic, Z. et al. (2017) 'Potential Influence of Selenium, Copper, Zinc and Cadmium on L-Thyroxine Substitution in Patients with Hashimoto Thyroiditis and Hypothyroidism', Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association, 125 (2), pp. 79–85.
Rayman, M.P., et al., 2014. Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: a randomised, controlled pilot trial. Br. J. Nutr. 112 (1), 99–111.
Ribas-Fitó, N., et al., 2002. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. Pediatr. Res. 52 (2), 163–167.
Ruggieri, S., et al., 2019. Three contaminated sites in southern Italy. The Neonatal Environment and Health Outcomes cohort: protocol for a longitudinal birth cohort study. BMJ Open 9 (6), e029471.
Ruggieri, S. et al. (2021) 'The Neonatal Environment and Health Outcomes (NEHO) Birth Cohort Study: Behavioral and Socioeconomic Characteristics and Drop-Out Rate from a Longitudinal Birth Cohort in Three Industrially Contaminated Sites in Southern Italy', International journal of environmental research and public health, 18(3). Available at: https://doi.org/10.3390/ijerph18031252.
Sala, M. et al. (2001) 'Levels of hexachlorobenzene and other organochlorine compounds in cord blood: exposure across placenta', Chemosphere, 43(4-7). Available at: https://doi.org/10.1016/s0045-6535(00)00450-1.
Sargis, R.M., Heindel, J.J., Padmanabhan, V., 2019. Interventions to Address Environmental Metabolism-Disrupting Chemicals: Changing the Narrative to Empower Action to Restore Metabolic Health. Front. Endocrinol. 10, 33.
Sclove, S.L., 1987. Application of model-selection criteria to some problems in multivariate analysis. Psychometrika 52 (3), 333–343.
Singhal, A. (2017) 'Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth', Annals of nutrition & metabolism, 70(3). Available at: https://doi.org/10.1159/000464302.
Smink, A., et al., 2008. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Pædiatrica 97 (10), 1465–1469.
Steinbrenner, H., 2013. Interference of selenium and selenoproteins with the insulin-regulated carbohydrate and lipid metabolism. Free Radic. Biol. Med. 65, 1538–1547.
Stratakis, N. et al. (2022) 'Prenatal exposure to persistent organic pollutants and childhood obesity: A systematic review and meta-analysis of human studies', Obesity reviews: an official journal of the International Association for the Study of Obesity, 23 Suppl 1(Suppl 1), p. e13383.
Svensson, K., et al., 2021. Prenatal exposures to mixtures of endocrine disrupting chemicals and children's weight trajectory up to age 5.5 in the SELMA study. Sci. Rep. 11 (1), 1–12.
Tang-Péronard, J.L., et al., 2014. Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands. Am. J. Clin. Nutr. 99 (1), 5–13.
Traina, A., et al., 2021. Organochlorines and Polycyclic Aromatic Hydrocarbons as fingerprint of exposure pathways from marine sediments to biota. Mar. Pollut. Bull. 170, 112676.
Valvi, D., et al., 2014. Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy. Obesity 22 (2), 488–496.
Venables, W.N., Ripley, B.D., 2013. Modern Applied Statistics with S. Springer Science & Business Media.
Verhulst, S.L., et al., 2009. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ. Health Perspect. 117 (1), 122–126.
Vicente-Villardon, J.L., Vicente-Gonzalez, L. and Frutos-Bernal, E. (2023) MultBiplotR. Available at: https://cran.r-project.org/web/packages/MultBiplotR/index.html.
Vogel, M. (2022) childsds: Data and Methods Around Reference Values in Pediatrics. Comprehensive R Archive Network (CRAN). Available at: https://CRAN.R-project.org/package=childsds (Accessed: 3 July 2024).
Warner, M. et al. (2018) 'Obesity in relation to serum persistent organic pollutant concentrations in CHAMACOS women', Environmental epidemiology (Philadelphia, Pa.), 2(4). Available at: https://doi.org/10.1097/EE9.0000000000000032.
Watson, C.V., et al., 2020. Characterization of trace elements exposure in pregnant women in the United States, NHANES 1999-2016. Environ. Res. 183, 109208.
Weis, K.E., et al., 2023. Pre- and postnatal developmental exposure to the polychlorinated biphenyl mixture aroclor 1221 alters female rat pituitary gonadotropins and estrogen receptor alpha levels. Reprod. Toxicol. 118, 108388.
WHO Child growth standards (2006) Child growth standards, Child growth standards. Available at: https://www.who.int/tools/child-growth-standards (Accessed: 3 July 2024).
WHO-a (2017) WHO. Available at: https://iris.who.int/handle/10665/259349 (Accessed: 3 July 2024).
WHO-b (2022) WHO. Available at: https://iris.who.int/bitstream/handle/10665/353747/9789289057738-eng.pdf?sequence=1 (Accessed: 3 July 2024).
Wright, C., et al., 2008. Implications of adopting the WHO 2006 Child Growth Standard in the UK: two prospective cohort studies. Arch. Dis. Child. 93 (7), 566.
Wu, W., et al., 2021. Maternal essential metals, thyroid hormones, and fetal growth: Association and mediation analyses in Chinese pregnant women. Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements 68, 126809.
Xiao, L., et al., 2022. Associations between serum copper, zinc, selenium level and sex hormones among 6-19 years old children and adolescents in NHANES 2013-2016. Front. Endocrinol. 13, 924338.
Yan, Y., et al., 2023. The effect of endocrine-disrupting chemicals on placental development. Front. Endocrinol. 14, 1059854.
Zhou, Y., Zhou, J., He, Y., Fang, J., Tang, J., Li, S., Guo, J., Luo, Q., Zhong, K., Huang, K., Chen, G., 2024 Mar. Associations between prenatal metal exposure and growth rate in children: Based on Hangzhou Birth Cohort Study. Sci Total Environ. 15 (916), 170164. https://doi.org/10.1016/j.scitotenv.2024.170164.
Zoroddu, M.A., et al., 2019. The essential metals for humans: a brief overview. J. Inorg. Biochem. 195, 120–129.
Zuk, A.M., Liberda, E.N., Tsuji, L.J.S., 2021. Environmental contaminant body burdens and the relationship with blood pressure measures among Indigenous adolescents using Bayesian Kernel Machine Regression: Results from the Nituuchischaayihtitaau Aschii: Multi-Community Environment-and-Health Study in Eeyou Istchee, Quebec, Canada, 2005–2009. Environ. Adv. 4, 100048.