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Defining the external exposome of newborns from La Palma Island, Spain: characteristics of realistic mixtures and its role on Precision Public Health

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ABSTRACT

Introduction: The exposome framework provides an integrative perspective to characterize real-life exposures beyond single-chemical assessments. However, evidence on perinatal exposomes in non-urban populations is limited, particularly regarding pollutant mixtures and their contribution to adverse birth outcomes.
Methods: We conducted a population-based cross-sectional study including 471 neonates from La Palma (Spain). A total of 106 pollutants were quantified in cord blood using validated methods. Exposures encompassed essential elements, toxic metals, prioritized pollutants, emerging elements, organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs), grouped into seven categories. Statistical analyses included descriptive statistics, correlation matrices, principal component analysis (PCA), and network visualization, stratified by sex, birthweight, and maternal smoking.
Results: Essential elements (Se, Zn, Cu, Mn) were detected in all samples, whereas emerging rare earth elements showed lower prevalence. PCA highlighted distinct exposure profiles, with PAHs and OCPs explaining the highest variance. Maternal smoking strongly influenced clustering: small for gestational age neonates from smoking mothers displayed a specific mixture of PAHs, OCPs, low-chlorinated PCBs, and Pb, contrasting with neonates of appropriate or large for gestational age. Network analyses revealed four main pollutant clusters, diverging from the seven predefined chemical groups and reflecting real-world mixtures shaped by common sources. Emerging pollutants, including rare earth elements and metals from electronic waste, formed a separate cluster.
Conclusion: Exposome-based approaches can characterize neonatal exposure mixtures, reveal modifiable patterns, and inform targeted interventions within Precision Public Health. These findings underscore the need to mitigate maternal smoking and address emerging contaminant exposures in perinatal populations.

1. Introduction

The term "exposome" encompasses the totality of environmental exposures encountered by an individual throughout their lifetime, including chemical, lifestyle, psychosocial, and physical factors (Wild, 2012; Vrijheid et al., 2021). This concept integrates both internal and external exposures, which are dynamic and continuously evolving across different life stages (Hohenblum et al., 2012). The exposome

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serves as a complementary framework to the genome, enhancing our understanding of disease etiology. Notably, environmental exposures can be as influential as genetic predispositions in disease development. Interactions between the exposome and genome are ongoing and play a crucial role in pathogenesis, predominantly mediated by epigenetic mechanisms (Wild, 2005; Alam et al., 2021).

There is substantial evidence indicating that chemical exposures during fetal and early life stages are associated with adverse outcomes, including impaired fetal growth, neurotoxicity, immunotoxicity, and obesogenic effects, which may manifest in childhood or even later in adulthood (Robinson et al., 2015). While extensive research has been conducted on the human genome, the exposome remains relatively underexplored, particularly at the population level. Despite the variability of individual external exposomes over a lifetime, it is possible to assess these exposures within a specific population in a defined geographical area. Comparative studies of individuals from the same region but with differing lifestyles have demonstrated the feasibility of such assessments (Henríquez et al., 2016, 2018).

Since the inception of the exposome concept, considerable efforts have been directed toward its characterization through analytical and toxicological studies. However, there is an increasing need to integrate exposome research into public health studies to facilitate the development of targeted public health policies (Precision Public Health). Through exposome-based research, precision public health initiatives can be implemented at a regional level to mitigate health risks associated with environmental exposures (Baker and Bjerregaard, 2023; Matus et al., 2024).

Several research projects focusing on the exposome aim to consolidate various environmental hazards to examine their associations with adverse health outcomes (Siroux et al., 2016). Pregnancy and birth cohort studies, in particular, provide a unique opportunity to investigate the exposome during highly susceptible developmental periods, such as early infancy. Importantly, disparities in environmental exposures may contribute to the formation of population subgroups with disproportionate exposure risks. For example, findings from the Human Early-Life Exposome (HELIX) Project revealed that social determinants, including social class, educational attainment, and occupational status, significantly influenced the exposome of pregnant women across different European cities, underscoring the role of residential area in shaping differential environmental risks (Vrijheid et al., 2014; Robinson et al., 2018).

Based on these premises, the present study was designed to comprehensively assess the chemical pollutant burden in newborns from La Palma, Canary Islands, Spain. We conducted a detailed toxicological analysis on umbilical cord blood samples collected at birth from nearly all infants born on the island over a one-year period (2015–2016; n = 471; 91.4%) (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a, 2019b). Our study aims to elucidate intra- and inter-group relationships among key environmental pollutants in this distinct newborn population, characterized by its relative geographic isolation and non-urban setting. By analyzing the correlation structure within the "newborn external exposome," we seek to explore the potential impact of pollutant mixtures on perinatal health outcomes. Ultimately, our findings will contribute to the development of precision public health strategies aimed at modifying the external exposome to diminish potential health risks associated with environmental exposures.

2. Material and methods

2.1. Study design and setting

This cross-sectional study was conducted on La Palma, the northwesternmost island of the Canary Archipelago, Spain. The Canary Islands, an autonomous Spanish region, are geographically located off the northwest coast of Africa but are fully integrated into the European Union (EU) as one of its "outermost regions" (Eurostat. Statistics Explained, 2024).

La Palma, situated in the Atlantic Ocean approximately 445 km from the African coast and about 1100 km from mainland Spain. It covers an area of 708 km^2 and has a population of approximately 85,000 inhabitants. The island's capital, Santa Cruz de La Palma, is home to around 15,000 residents and houses the only public hospital that provides care for all pregnant women at the time of delivery (Gobierno de Canarias, 2023).

2.2. Study population

A detailed description of the study population, ethical approval and design has been previously published (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a). In brief, between March 1, 2015, and April 30, 2016, a total of 516 pregnant women from the general population were recruited at La Palma Public Hospital during labor. Both parents provided signed informed consent to participate in the study and completed a brief questionnaire. Due to maternal refusal, sample unavailability, or incomplete data collection at birth, 8.6% of births were excluded. Ultimately, data from 471 neonates were included, representing a nearly complete population-based sample for the island.

2.3. Data collection

To characterize the newborns' external exposome, data were collected through multiple sources, including biological sampling, maternal questionnaires. A semi-quantitative, self-administered questionnaire was completed by the mothers at La Palma Public Hospital upon admission to the obstetrics unit prior to delivery.

The study incorporated 82 exposure variables:

- Chemical pollutants in cord blood (n = 64)
- Maternal dietary variables (n = 7): fruit, meat, vegetables, dairy, and fish consumption, as well as consumption of organic food and type of water consumed (Ramón et al., 1994)
- Lifestyle-related exposures (n = 5): maternal and paternal occupation, maternal and paternal pesticide exposure, and housing characteristics (type and age)
- Maternal-related variables (n = 6): presence of maternal diseases, smoking status, previous abortions, previous pregnancies, and history of breastfeeding.

2.4. Toxicological analyses and exposome assessment

The quantification of a total of 106 chemical contaminants in cord blood samples was performed using validated analytical methods, as detailed in prior publications (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a). These contaminants included inorganic pollutants such as 18 trace metals prioritized by the Agency for Toxic Substances and Disease Registry (ATSDR) (Centers for Disease Control and Prevention (CDC), 2023): Ag (silver), As (arsenic), Ba (barium), Be (berillium), Cd (cadmium), Cr (chromium), Cu (copper), Hg (mercury), Ni (nickel), Pb (lead), Sb (antimony), Se (selenium), Sr (strontium), Th (thorium), Tl (tallium), U (uranium), V (vanadium), and Zn (zinc). Additionally, 26 emerging inorganic pollutants, not classified as priority by the ATSDR, were also quantified: Au (gold), Bi (bismuth), Ce (cerium), Dy (dysprosium), Eu (europium), Er (erbium), Ga (gallium), Gd (gadolinium), Ho (holmium), In (indium), La (lanthanum), Lu (lutetium), Nb (niobium), Nd (neodimium), Os (osmium), Pd (palladium), Pr (praseodymium), Pt (platinum), Ru (ruthenium), Sn (tin), Sm (samarium), Ta (tantalum), Tb (terbium), Tm (thulium), Y (Ytrium), and Yb (ytterbium).

In addition to inorganic pollutants, the burden of persistent organic pollutants (POPs) was assessed, including 20 organochlorine pesticides (OCPs) (aldrin, dieldrin, endrin, endosulfan-α, endosulfan-β, endosulfan sulfate, HCB, heptachlor, lindane, methoxychlor, mirex, o'p-DDD, o'p-

DDE, o'p-DDT, p'p-DDD, p'p-DDE, p'p-DDT, α-HCH, β-HCH, and δ-HCH); 18 polychlorinated biphenyl (PCB) congeners (PCB-101, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-138, PCB-153, PCB-156, PCB-157, PCB-167, PCB-180, PCB-189, PCB-28, PCB-52, PCB-77, PCB-81); 8 brominated diphenyl ethers (BDEs) (BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183); and 16 polycyclic aromatic hydrocarbons (PAHs) (acenaphthalene, acenaphthene, anthracene, benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(g,h,i)perylene, benzo(k)fluoranthene, chrysene, dibenzo(a,h) anthracene, fluoranthene, fluorene, indene(1,2,3-cd)pyrene, naphthalene, phenanthrene, pyrene). These analyses resulted in the quantification of 44 inorganic and 62 organic contaminants in cord blood samples (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a, 2019b). Detailed methodologies for sample collection, treatment, validated analytical procedures, and quality control measures have been previously reported (Henríquez et al., 2018, 2020).

2.5. Statistical analysis

Statistical analyses were conducted using a preexisting dataset from our prior research (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a, 2019b). For the purposes of the present study, only those contaminants detected in more than 40 newborns were included in the analysis, resulting in a final set of 64 pollutants out of the 106 initially quantified.

To facilitate interpretation, pollutants were classified into seven predefined groups according to chemical structure, and toxicological or physiological profiles, as detailed in previous studies (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a; Wang et al., 2024; Eguchi et al., 2022; Hoover et al., 2023). The final dataset comprised 64 pollutants:

Group 1A: Essential trace elements involved in human nutrition and physiology (Co, Cr, Cu, Fe, Mn, Mo, Ni, Se, Zn).
Group 1B: Highly toxic metals and metalloids (As, Cd, Hg, Pb).
Group 1C: Inorganic contaminants classified as priority pollutants by the ATSDR (Ag, Ba, Be, Sb, Sr, Th, Tl, U, V).
Group 2: Emerging inorganic pollutants (Al, Au, Bi, Ce, Er, Eu, Ga, Ho, In, La, Lu, Nb, Nd, Os, Pr, Pt, Ru, Si, Sm, Sn, Ta, Tb, Ti, Tm, Y).
Group 3: Organochlorine compounds and derivatives (dieldrin, HCB, p'p-DDE, β-HCH).
Group 4: Polychlorinated biphenyl congeners (PCB-28, PCB-52, PCB-101, PCB-118, PCB-123, PCB-126, PCB-138, PCB-153, PCB-180).
Group 5: Polycyclic aromatic hydrocarbons (fluoranthene, fluorene, naphthalene, phenanthrene, pyrene).

Categorical variables were summarized as absolute frequencies and percentages, and associations were tested using the χ^2 test. Continuous variables were expressed as means with standard deviations, accompanied where relevant by 95% confidence intervals, and as medians with interquartile ranges (P25–P75). Normality was assessed using the Kolmogorov–Smirnov or Shapiro–Wilk test. For comparisons across three independent groups, the non-parametric Kruskal–Wallis test was applied, followed by pairwise comparisons using the Dwass–-Steel–Critchlow–Fligner (DSCF) method when appropriate. Statistical significance was set at $p < 0.05$. Analyses were performed using R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) and Jamovi (version 2.6; The Jamovi Project, 2025).

2.5.1. Principal Component Analysis (PCA)

Within each pollutant group, PCA was performed to reduce dimensionality while preserving the majority of variance. Retention of components followed the Kaiser criterion (eigenvalues >1) and scree plot inspection. PCA was considered informative only when the first three components jointly explained more than 60% of the variance.

2.5.2. Network analysis and inter-group correlation matrices

To investigate co-exposure patterns, Spearman correlation coefficients were calculated for all pollutant pairs. Network graphs were constructed for the full dataset and stratified according to birthweight categories defined by gestational age and sex: Small for Gestational Age (SGA, birthweight <10th percentile), Appropriate for Gestational Age (AGA, birthweight between the 10th and 90th percentiles), and Large for Gestational Age (LGA, birthweight >90th percentile), as well as by maternal smoking status. In these graphs, nodes represent individual pollutants and edges connect pairs with $|\rho| \geq 0.4$, indicating strong associations. Highly correlated pollutants appear clustered, while weakly or uncorrelated ones are positioned farther apart. Network visualizations were generated using the igraph package in R.

Median absolute inter-group correlations were also computed. For each pair of pollutant groups, all possible pairwise correlations were calculated, absolute values were taken, and the median was used as the representative measure of association. Global matrices were generated for the entire cohort, and subgroup-specific matrices were created for smokers vs. non-smokers and by birthweight category, enabling identification of group-specific co-occurrence patterns.

3. Results

3.1. Characteristics of the study population and exposure values

The study included 471 mother-newborn pairs. The mean maternal age was 32 years (IQR: 27–35), with no significant differences between birth weight groups ($p = 0.1057$). The majority of mothers were non-smokers (88.7%), while 11.3% reported active smoking during pregnancy. Smoking prevalence was significantly higher among mothers of SGA neonates (21.3%) compared to those of AGA (9.3%) and LGA (17%) neonates ($p = 0.0207$).

Regarding parity, 38.2% of mothers were primiparous, with a significantly higher proportion among SGA neonates (46.8%) compared to 39.3% in the AGA group and 21.3% in the LGA group ($p = 0.0253$). The number of previous pregnancies also differed significantly ($p = 0.0047$), with 46.8% of SGA neonates born to mothers with only one previous pregnancy, compared to 39.3% in the AGA group and 21.3% in the LGA group. In contrast, the proportion of mothers with three or more previous pregnancies was significantly higher in the LGA group (48.9%) compared to the SGA (19.1%) and AGA groups (23.9%). The history of miscarriages did not significantly differ between groups ($p = 0.2705$).

The median duration of residence on the island was 27 years (IQR: 18–32), with significant differences among groups ($p = 0.0206$). Mothers of SGA neonates had a longer residence (30 years, IQR: 24–34) compared to 26 years (IQR: 17–32) in the AGA group and 29 years (IQR: 14–33) in the LGA group. However, whether the mother had lived on La Palma her entire life was not associated with neonatal birth weight ($p = 0.3401$). Similarly, maternal diabetes was not significantly associated with birth weight ($p = 0.1191$).

More than half of the newborns were female (52.9%), with a significantly lower proportion in the LGA group (36.2%) compared to the AGA group (55.7%) ($p = 0.0278$). While the proportion of females in the SGA (46.8%) and AGA groups did not differ significantly ($p = 0.3174$), males were significantly more frequent in the LGA group ($p = 0.017$).

Significant differences were observed in birth weight categories ($p < 0.001$), with 10% of neonates classified as SGA (IQR: 2295–2540 g), 80% as AGA (IQR: 3030–3540 g), and 10% as LGA (IQR: 3950–4145 g). Similarly, significant differences were observed in birth length ($p < 0.001$), with 15.7% of neonates classified as low birth length (IQR: 46–47 cm), 69% as normal birth length (IQR: 49–50 cm), and 14.2% as high birth length (IQR: 52–53 cm). The median gestational age was 40 weeks (IQR: 39–41), and the median head circumference was 34 cm (IQR: 34–35). Apgar scores were consistently high in most of the newborns (Table 1).

Table 1
Sociodemographic characteristics according to birth weight of newborn.

	Total (n = 471) n (%)	SGA (n = 47) n (%)	AGA (n = 377) n (%)	LGA (n = 47) n (%)	p value
Maternal characteristics					
Age (years)	32 (8)	32 (9)	31 (8)	33 (7)	0.106
Residence area (Southern part of the island)	305 (64.8)	26 (55.3)	250 (66.3)	29 (61.7)	0.297
Residence (years)	27 (14)	30 (9)	26 (15)	29 (19)	0.021
Vaginal Delivery	351 (74.5)	29 (61.7)	286 (75.9)	36 (76.6)	0.104
Parity (Primiparous)	180 (38.2)	22 (46.8)	148 (39.3)	10 (21.3)	0.025
Miscarriages[a] (yes)	129 (27.4)	11 (23.4)	99 (26.3)	19 (40.4)	0.099
Disease[b] (yes)	130 (27.6)	12 (25.5)	104 (27.6)	14 (29.8)	0.899
Smoking (yes)	53 (11.3)	10 (21.3)	35 (9.3)	8 (17.0)	0.021
Infant characteristics					
Gestational age (weeks)	40 (2)	37 (2.5)	40 (2)	40 (1)	<0.001
Sex (male)	222 (47.1)	25 (53.2)	167 (44.3)	30 (63.8)	0.028
Birth weight (g)	3260 (625)	2410 (245)	3260 (510)	4030 (195)	<0.001
Length (cm)	49.5 (3)	46 (2)	49 (2)	52 (2)	<0.001
Head circumference (cm)	34 (1)	33 (1)	34 (1)	36 (1)	<0.001
Malformation[c] (yes)	46 (9.8)	3 (6.4)	36 (9.5)	7 (14.9)	0.362
Apgar 1 score 7-8	43 (9.1)	8 (17.0)	32 (8.5)	3 (6.4)	0.278
Apgar 5 score 8	5 (1.1)	1 (2.1)	4 (1.1)	0 (0.0)	0.603

Abbreviations: SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.
[a]Kruskal-Wallis tests; median and range were reported.
[b]Chi squared test; absolutely frequency and percentage were reported.
[a] Data referred to previous pregnancies.
[b] Include diabetes, arterial hypertension and hypothyroidism.
[c] Include cardiac, oral, urogenital, skin, orthopedic and other malformations.

The dietary habits of the mothers were analyzed in relation to neonatal birth weight. No significant associations were found between birth weight categories and the consumption of fruits, vegetables, meat, fish, organic food, or water type. However, milk consumption was significantly associated with birth weight (p = 0.0022) (Table 1S). Among mothers of SGA neonates, 72.3% reported high milk consumption, compared to 70.6% in the AGA group and 61.7% in LGA group. Conversely, low milk consumption was more frequent in mothers of LGA neonates (19.1%) and SGA neonates (21.3%), compared to 8.0% in the AGA group.

3.2. Levels of pollutants on cord blood samples

The concentrations of contaminants in the 471 cord blood samples have been previously reported by our research group (Cabrera-Rodriguez et al., 2018; Cabrera-Rodríguez et al., 2019a, 2019b).

A summary of the key findings is presented below.

3.2.1. Inorganic pollutants

A total of 47 inorganic elements were quantified in the cord blood samples (Table 2), ten of which—As, Co, Cu, Fe, Mn, Mo, Sb, Se, Sr, and Zn—were detected in 100% of samples. In contrast, the least frequently detected elements were Be (20%), Er (24.8%), Lu (18.3%), and Ta (22.1%).

As expected, the elements detected at the highest concentrations were the essential trace elements Cu, Se, Zn, and Sr. The median levels of As, Ba, Cr, Pb, and Sb exceeded 0.5 ng/mL in all cases.

Among the emerging inorganic pollutants, Dy, Gd, and Yb were detected in <10% of samples (Supplementary Table S2).

3.2.2. Organic pollutants

The concentrations of organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and other organic contaminants are summarized in Table 3. Among the OCPs, p,p′-DDE and hexachlorobenzene (HCB) were the most frequently detected, with detection rates of 98.7% and 79.9%, respectively. p,p′-DDE exhibited the highest median concentration (0.15 ng/mL), followed by lindane (0.111 ng/mL, detection frequency: 2.7%) (Supplementary Table S3).

A total of 18 PCB congeners were analyzed in 447 cord blood samples. As expected, those with the highest detection frequencies and concentrations were PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180. Among them, PCB-28 and PCB-153 were the most frequently detected congeners, with detection rates of 65.3% and 62.6%, respectively. The highest median concentration was observed for PCB-28 (0.11 ng/mL), followed by PCB-52 (0.055 ng/mL), with the latter detected in 49.7% of samples.

3.3. Correlations of pollutant groups within the study population

In the overall sample, pollutants within the same pre-assumed groups exhibited stronger correlations compared to those across different groups. However, inter-group correlations rarely exceeded 0.4, indicating limited cross-group associations.

Sex-based comparisons revealed that correlation patterns among pollutant groups in male and female neonates were largely similar to those observed in the total sample. However, organic pollutants (OCPs, PCBs, and PAHs) showed higher correlations in females (0.30, 0.24, and 0.31, respectively) compared to males (0.24, 0.18, and 0.18, respectively) (Fig. 1).

Maternal smoking influenced pollutant correlations significantly (Fig. 2). Neonates born to smoking mothers exhibited the highest median correlation between OCPs and PCBs (0.33) and between OCPs and PAHs (0.47), suggesting increased co-exposure to these compounds.

Birth weight was also associated with pollutant interaction patterns (Fig. 3). SGA neonates displayed the highest correlations between toxic inorganic pollutants (Group 1B) and OCPs (0.36), as well as PAHs (0.45), compared to AGA and LGA neonates, suggesting differential pollutant accumulation patterns in this subgroup.

3.4. Principal component analyses (PCA)

The first principal component (PC1) explained varying proportions of pollutant variance across maternal smoking status and neonatal birth weight categories (Supplementary Table S4**)**.

3.4.1. Maternal smoking and pollutant variance

Essential trace elements (Group 1A) exhibited higher variance in non-smokers (47.73%) than in smokers (43.43%), with Zn, Se, and Mn contributing most. Conversely, toxic metals (Group 1B) showed greater

Table 2
Quantitative concentrations of inorganic elements in cord blood samples (ng/mL).

Group	Element	Percentage Detected (n = 471)	Median	Percentile 25 –75	95% CI (lower–upper)
1A	Co (Cobalt)	100.0	0.17	0.12–0.24	0.18–0.20
	Cr (Chromium)	98.1	1.00	0.71–1.37	1.06–1.18
	Cu (Copper)	100.0	367.77	270.99–496.83	384.48–419.60
	Fe (Iron)	100.0	3321.21	2096.67–6027.75	5025.67–6295.49
	Mn (Manganese)	100.0	2.85	2.09–3.80	3.04–3.34
	Mo (Molybdenum)	100.0	1.10	0.82–1.50	1.18–1.31
	Ni (Nickel)	92.4	0.66	0.35–1.07	0.76–0.93
	Se (Selenium)	100.0	62.09	49.45–81.35	64.49–68.89
	Zn (Zinc)	100.0	1162.90	865.51–1454.92	1141.27–1216.97
1B	As (Arsenic)	100.0	0.59	0.30–1.30	1.09–1.64
	Cd (Cadmium)	65.0	0.02	0.01–0.02	0.02–0.02
	Hg (Mercury)	99.4	0.67	0.42–1.05	0.76–0.86
	Pb (Lead)	89.8	1.04	0.33–2.20	1.58–2.03
1C	Ag (Silver)	95.5	0.05	0.03–0.11	0.11–0.20
	Ba (Barium)	96.8	1.67	0.83–2.70	1.87–2.38
	Be (Beryllium)	20.0	0.10	0.06–0.12	0.09–0.11
	Sb (Antimony)	100.0	11.22	7.39–16.86	12.94–14.69
	Sr (Strontium)	100.0	37.07	27.56–51.61	39.28–42.90
	Th (Thorium)	57.1	0.01	0.01–0.02	0.01–0.02
	Tl (Thallium)	56.1	0.02	0.01–0.02	0.02–0.02
	U (Uranium)	57.3	0.01	0.01–0.03	0.03–0.05
	V (Vanadium)	99.8	0.17	0.11–0.29	0.22–0.26
2	Al (Aluminum)	64.3	5.20	2.40–9.14	6.50–11.75
	Au (Gold)	52.4	0.01	0.01–0.02	0.02–0.02
	Bi (Bismuth)	36.1	0.03	0.01–0.05	0.03–0.05
	Ce (Cerium)	92.8	0.04	0.02–0.06	0.05–0.07
	Er (Erbium)	24.8	0.01	0.01–0.01	0.01–0.02
	Eu (Europium)	57.3	0.01	0.01–0.06	0.03–0.03
	Ga (Gallium)	70.9	0.03	0.02–0.06	0.04–0.04
	Ho (Holmium)	46.1	0.01	0.01–0.27	0.09–0.12
	In (Indium)	27.2	0.01	0.01–0.03	0.02–0.03
	La (Lanthanum)	76.0	0.02	0.01–0.03	0.02–0.09
	Lu (Lutetium)	18.3	0.05	0.04–0.05	0.04–0.05
	Nb (Niobium)	66.0	0.01	0.01–0.02	0.02–0.02
	Nd (Neodymium)	55.4	0.01	0.01–0.02	0.01–0.02
	Os (Osmium)	50.7	0.02	0.01–0.03	0.02–0.03
	Pr (Praseodymium)	37.4	0.01	0.01–0.02	0.02–0.02
	Pt (Platinum)	57.1	0.01	0.01–0.04	0.03–0.05
	Ru (Ruthenium)	42.5	0.01	0.01–0.01	0.01–0.03
	Si (Silicon)	80.9	9387.23	3319.47–41667.77	27691.25–35491.02
	Sm (Samarium)	29.9	0.03	0.02–0.04	0.03–0.03
	Sn (Tin)	82.6	0.26	0.13–0.54	0.38–0.54
	Ta (Tantalum)	22.1	0.01	0.01–0.02	0.02–0.03
	Tb (Terbium)	47.3	0.02	0.01–0.03	0.02–0.02
	Ti (Titanium)	98.9	5.17	3.82–7.12	5.44–5.98
	Tm (Thulium)	43.5	0.02	0.01–0.03	0.02–0.02
	Y (Yttrium)	60.9	0.01	0.01–0.02	0.02–0.02

Abbreviation: CI, confidence interval. Note: Elements detected in fewer than 40 newborns are reported in Supplementary Table S2.

variance in smokers (36.81%) than in non-smokers (33.46%), primarily driven by Cd (0.69 vs. 0.46) and Hg (0.59 vs. 0.56), whereas Pb had a significantly higher contribution in non-smokers (0.57 vs. 0.05, $p < 0.05$).

PCBs (Group 4) exhibited opposite loading patterns, with PCBs 101, 28, and 52 showing positive values in smokers but negative values in non-smokers, suggesting differential sources or metabolism. PAHs (Group 5) had the highest variance, particularly in smokers (88.62%) compared to non-smokers (80.52%), reflecting greater exposure. Organochlorine pesticides (Group 3) maintained consistent variance (~48%) in both groups, with HCB, dieldrin, and p,p'-DDE as key contributors.

3.4.2. Neonatal birth weight and pollutant variance

Essential trace elements (Group 1A) showed the highest variance in LGA, 59.90% and SGA, 56.96% neonates, while AGA neonates exhibited lower variance (44.51%) and predominantly negative loadings, suggesting metabolic differences.

Toxic metals (Group 1B) contributed most to SGA neonates (47.89%), with Hg (0.64) and As (0.58) being primary drivers. AGA neonates exhibited the lowest variance (31.94%), while LGA neonates showed intermediate levels (38.57%), with Cd (0.64) and Pb (0.51) as dominant contributors.

Priority inorganic pollutants (Group 1C) exhibited the highest variance in SGA neonates (29.41%), with Pd, Tl, and Th showing the strongest loadings. While AGA neonates had predominantly negative loadings, LGA neonates demonstrated a more balanced pollutant distribution.

Organochlorine pesticides (Group 3) were most prominent in SGA neonates (54.73%), with HCB (0.62) and β-HCH (0.59) contributing most, while p,p'-DDE (0.50) had the highest loading in AGA neonates.

PAHs (Group 5) demonstrated the highest overall variance, particularly in SGA neonates (91.09%), followed by AGA (80.75%) and LGA (74.83%), highlighting broad prenatal exposure.

3.5. Network analyses

Network visualization of pollutant interactions in newborns revealed four distinct clusters of pollutants, differing from the seven pre-defined groups based on chemical classification (Fig. 4A–D). These clusters formed strong interconnections regardless of chemical structure or toxicological properties.

Table 3
Quantitative concentrations of organic elements in cord blood samples (ng/mL).

Group	Element	Percentage Detected % (n = 447)	Median	Percentile 25–75	95% CI (lower–upper limit)
3	Dieldrin	25.3	0.11	0.06 – 0.20	0.12 – 0.17
	HCB	79.9	0.04	0.03 – 0.06	0.05 – 0.05
	p,p'-DDE	98.7	0.15	0.08 – 0.24	0.20 – 0.27
	β-HCH	19.9	0.06	0.05 – 0.09	0.06 – 0.12
4	PCB 28	65.3	0.11	0.05 – 0.29	0.21 – 0.29
	PCB 52	49.7	0.05	0.03 – 0.09	0.06 – 0.08
	PCB 101	53.0	0.04	0.02 – 0.08	0.05 – 0.06
	PCB 118	10.5	0.04	0.03 – 0.08	0.05 – 0.07
	PCB 123	9.6	0.04	0.02 – 0.07	0.04 – 0.06
	PCB 138	47.2	0.04	0.03 – 0.08	0.05 – 0.06
	PCB 153	62.6	0.04	0.03 – 0.09	0.05 – 0.06
	PCB 180	33.3	0.03	0.03 – 0.05	0.04 – 0.05
5	Fluoranthene	36.9	0.17	0.08 – 0.27	0.18 – 0.24
	Fluorene	42.5	0.12	0.06 – 0.21	0.13 – 0.18
	Naphthalene	28.0	1.19	0.61 – 2.94	1.82 – 2.92
	Phenanthrene	57.7	0.38	0.18 – 1.06	0.63 – 0.94
	Pyrene	55.7	0.15	0.07 – 0.28	0.17 – 0.22

Abbreviations: CI, Confidence Interval; HCB, hexachlorobenzene; p,p′-DDE, dichlorodiphenyldichloroethylene (p,p′-isomer); β-HCH, beta-hexachlorocyclohexane; PCB, polychlorinated biphenyl; PCB 28, 2,4,4′-trichlorobiphenyl; PCB 52, 2,2′,5,5′-tetrachlorobiphenyl; PCB 101, 2,2′,4,5,5′-pentachlorobiphenyl; PCB 118, 2,3′,4,4′,5-pentachlorobiphenyl; PCB 123, 2′,3,4,4′,5-pentachlorobiphenyl; PCB 126, 3,3′,4,4′,5-pentachlorobiphenyl; PCB 138, 2,2′,3,4,4′,5′-hexachlorobiphenyl; PCB 153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; PCB 180, 2,2′,3,4,4′,5,5′-heptachlorobiphenyl. Note: Elements detected in fewer than 40 newborns are reported in Supplementary Table S3.

In the overall network (Fig. 4A), four main communities were identified. The first cluster comprised a mixture of OCPs, PAHs, and lower chlorinated PCBs, including dieldrin, fluoranthene, naphthalene, pyrene, fluorene, phenanthrene, and PCBs 118, 28, 52, and 101. The second cluster primarily included OCPs and higher chlorinated PCBs, notably DDE, HCB, and PCBs 153, 138, and 180. Third cluster grouped rare earth elements and emerging inorganic pollutants (Al, Bi, Sn, Si, Th, Ho, Eu, Ce, Tb, In, Pr, Lu, Sm, Nb, Y, La, U, Nd, Ta, Er, Yb, Dy), while a fourth cluster comprised essential trace elements and toxic metals (Fe, Sb, Sr, Mo, Cu, Se, Co, Zn, Mn, Ba, Tl, Ni, Pb, Cd, Hg, As). Several pollutants appeared isolated, notably PCB 123, β-HCH, Ag, Be, and Pd.

When stratifying by birth weight, the networks displayed marked variations. Among SGA newborns (Fig. 4B), the network became denser, with rare earth elements (Group 2) closely connected to trace elements (Group 1A), while toxic metals such as Pb, Cd, Hg, and As occupied central positions linking metals with organic pollutants; in addition, PCBs, PAHs, and DDT-related compounds formed a distinct but connected cluster. In contrast, the network of AGA newborns (Fig. 4C) exhibited clearer separation of communities, with rare earth elements forming an independent cluster with limited links to trace elements, essential elements (Co, Zn, Fe, Mn, Cu, Se) grouping into a compact cluster, and organic pollutants forming a separate subnetwork, while PCB 123 and Be remained as isolated nodes. Additionally, in LGA newborns (Fig. 4D), rare earth elements displayed strong internal connectivity, trace elements (Zn, Fe, Co, Se, Mn) maintained a central subnetwork, and organic pollutants (PCBs, PAHs, and DDT metabolites) clustered independently from metals, with several pollutants—including PCB 123, Ag, Be, and Pd—remaining isolated nodes.

In smokers, a notable shift in network topology was observed. Specifically, clusters associated with organic pollutants (OCPs, PCBs, and PAHs) merged into a single, highly interconnected node, suggesting increased co-exposure in this group. Additionally, several toxic metals, including Pb, Cd, and Hg, displayed stronger links within the merged cluster, highlighting a potential cumulative effect of smoking-related pollutant exposure (Fig. 5A).

Conversely, in non-smokers, pollutants were organized into four distinct clusters, similarly to overall sample, with strong intra-group connections and a structured distribution of inorganic pollutants, organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs). The clustering remained consistent and well-delineated, with rare earth elements and toxic metals forming separate groups without major cross-contamination (Fig. 5B).

4. Discussion

This study successfully characterized the external exposome in a relatively isolated, non-urban population at a critical developmental stage—the perinatal period. In line with Precision Public Health

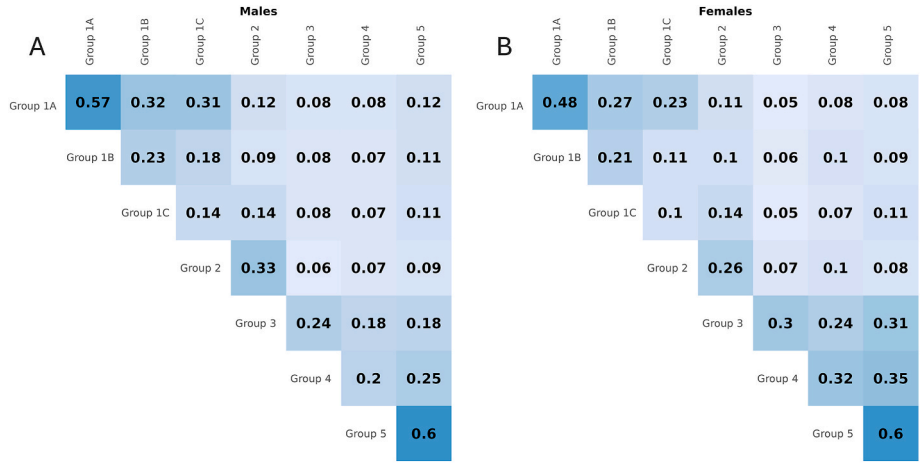

Fig. 1. Heatmap of correlation coefficients between elemental exposure groups, stratified by sex: male (A) and female (B).

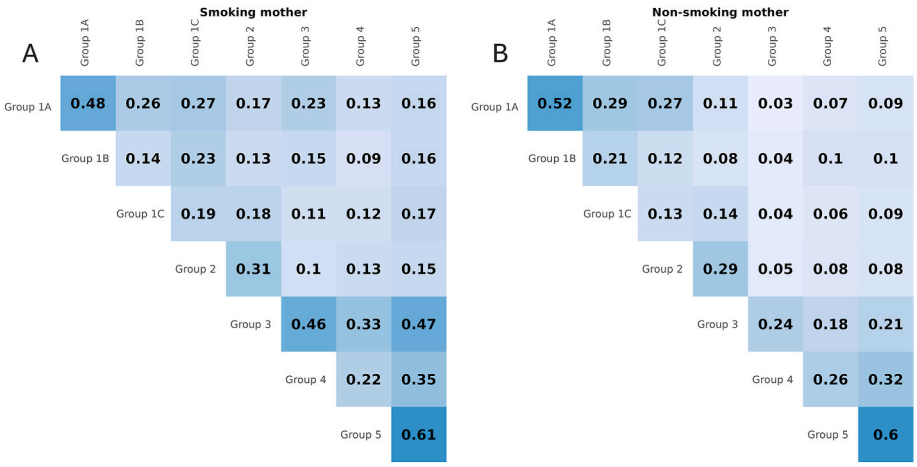

Fig. 2. Comparison of inter-group elemental correlations between maternal smoking: smokers (A) and non-smokers (B).

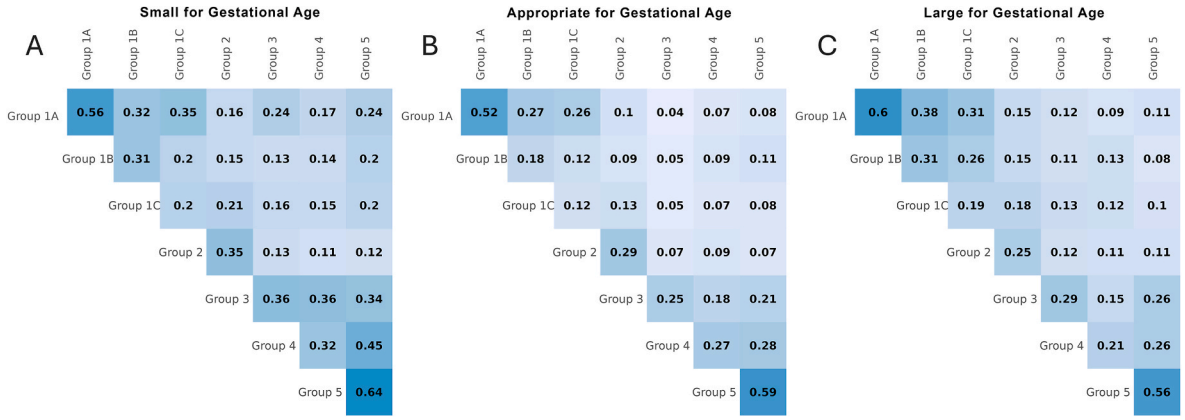

Fig. 3. Birth weight–dependent variations in elemental exposure correlations: small (A), appropriate (B), and large (C) for gestational age.

principles, defining population-specific exposome is essential for designing targeted public health interventions to mitigate exposure-related health risks. Unlike the genome, which is largely static, the external exposome is modifiable, providing an opportunity to prevent environmentally driven health effects (Zhang et al., 2025).

Our results demonstrate the utility of network and heat map methodologies in identifying pollutant clusters in human biomonitoring (HBM) studies. These techniques allow for the recognition of actual pollutant mixtures in a population without the constraints of predefined chemical or toxicological classifications. As suggested by Ottenbros et al. (2021) (Ottenbros et al., 2021), network visualization facilitates the identification of pollutant communities, enabling cross-study comparisons and the detection of shared exposure sources or pathway effects. This is particularly relevant given that biological effects of real-life pollutant mixtures may differ significantly from theoretical assumptions (Boada et al., 2012).

Initially, we categorized pollutants into seven groups based on chemical and toxicological properties, assuming shared exposure sources within each group. However, our findings revealed unexpected clustering patterns, with pollutants organizing into four distinct groups rather than the anticipated seven. These real-world mixtures suggest that common exposure sources, rather than chemical properties, may play a defining role. If confirmed, this insight could have significant public health implications, as eliminating specific exposure sources may prevent the adverse effects associated with entire pollutant mixtures.

Despite this, chemical structure remains a key determinant in pollutant clustering. As seen in previous studies (Wang et al., 2024), a well-defined PAH cluster emerged across all networks, likely due to shared environmental sources and similar toxicokinetic. However, a notable finding was the inclusion of dieldrin and low-chlorinated PCBs (28, 52, 101, and 118) within the PAH cluster. This underscores the need to consider co-exposure to these compounds when assessing PAH-related health risks. The specific congener profile of PCBs also warrants attention, as Songül et al. (2024) and Eguchi et al. (2022) (Eguchi et al., 2022; Yalçin et al., 2024) highlight the differential impacts of individual congeners on fetal development.

While PCBs were expected to cluster together due to their structural and toxicokinetic similarities (Ottenbros et al., 2021), our results showed a bifurcation: lower-chlorinated PCBs (28, 52, 101, 118) grouped with PAHs, whereas higher-chlorinated PCBs (138, 153, 180) clustered with OCPs (p'p-DDE and HCB). This suggests that M-PCBs (marker congeners 28, 52, 101, 118, 138, 153, and 180) may originate from distinct sources within the study population. Furthermore, PCB-123, a dioxin-like congener, remained unclustered, showing no strong associations with other pollutants. The detection of PCBs in newborns from a non-urban environment is concerning, given their well-documented endocrine, reproductive, neurological, and immunological effects (Van den Berg et al., 2006). Particularly, dioxin-like PCBs (DL-PCBs) are classified as human carcinogens by the IARC (Lauby-Secretan et al., 2016), making the presence of DL-PCB-123 in the external exposome of these neonates particularly alarming (Rodgers et al., 2018).

Beyond PCBs and OCPs, endocrine disruption emerged as a key concern. Both PCBs and OCPs interfere with hormone regulation, metabolic programming, and fetal development. PAHs, particularly low-molecular-weight PAHs, also exhibit endocrine-disrupting properties and can cross the placental barrier, raising concerns for long-term

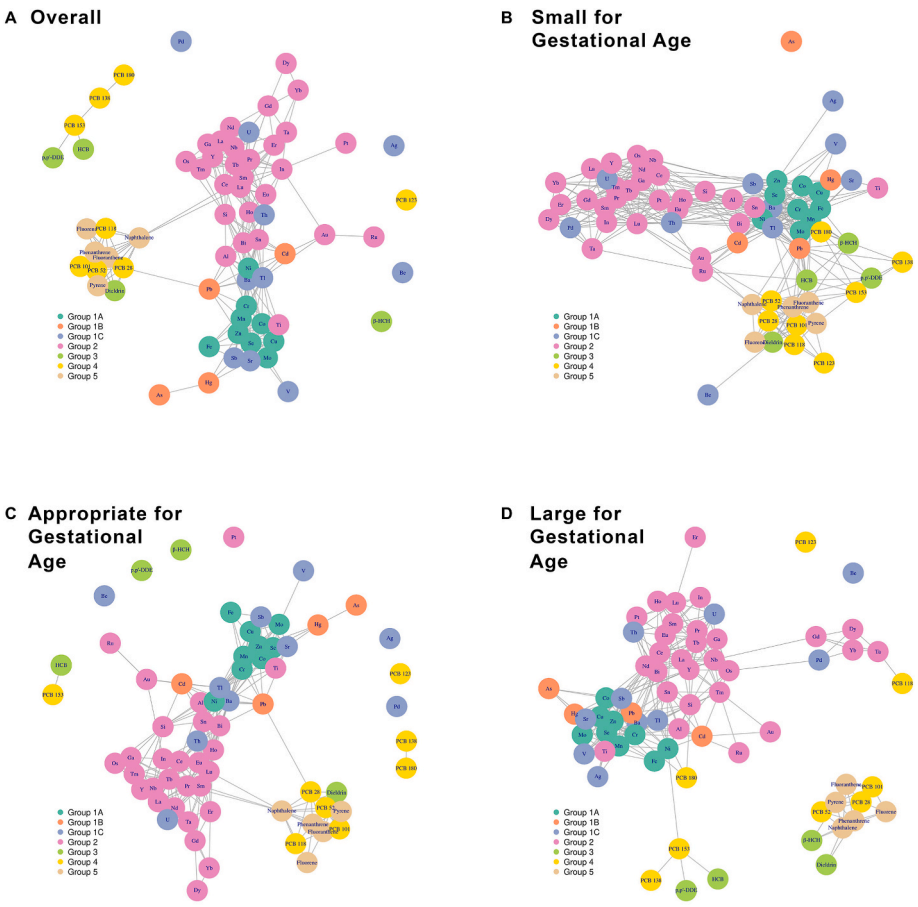

Fig. 4. Network-based clustering of pollutants in newborns compared to predefined chemical classification. Panels show clustering for (A) all newborns, (B) small, (C) appropriate, and (D) large for gestational age.

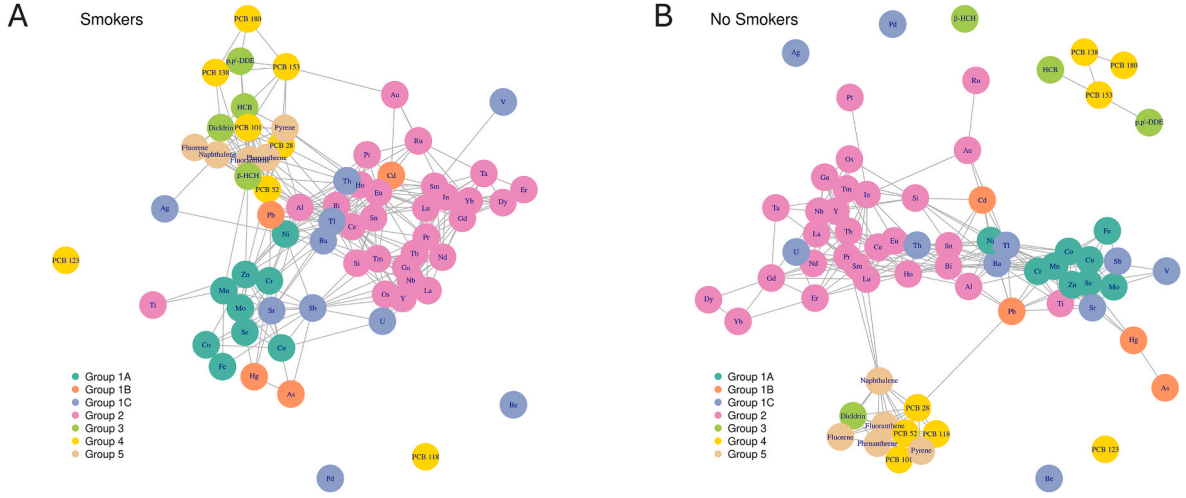

Fig. 5. Network-based clustering of pollutants in cord blood: smokers (A) vs. non-smokers (B).

impacts on child health (Rahman et al., 2023).

Additionally, our study identified a third major mixture, consisting of toxic metals with endocrine-disrupting properties, including Pb, Mo, Mn, Hg, Cu, Cs, Co, Cd, and As (Midya et al., 2022). These metals have also been implicated in oxidative stress, which can impair placental function, leading to intrauterine growth restriction (Hoover et al., 2023). In this sense, Cr, Ni, and Sb were negatively associated with fetal growth in this population (Cabrera-Rodriguez et al., 2018). Beyond endocrine disruption, metals are known to interact, affecting brain development through oxidative stress and altered neurotransmitter signaling (Thilakaratne et al., 2024). Given that metals often share environmental and dietary sources, public health interventions targeting metal exposure could simultaneously mitigate multiple risks.

A particularly concerning finding was the strong association of Pb with pollutant clusters in neonates of smoking mothers. Given that no safe blood Pb level has been established in children (Centers for Disease

Control and Prevention (CDC), 2024), our results underscore the urgent need for intervention to modify the neonatal exposome and prevent long-term cognitive impairments.

Adding to these concerns, we also identified a cluster of emerging pollutants, including rare earth elements (REEs) and metals used in electronic devices (Al, Bi, Sn, Si, Th, Ho, Eu, Ce, Tb, In, Pr, Lu, Sm, Nb, Y, La, U, Nd, Ta, Er, Yb, and Dy). While data on their toxicological effects remain limited, recent studies suggest that elevated REE concentrations are associated with SGA (Qiu et al., 2024).

4.1. Exposome variation in SGA neonates and maternal smoking

Beyond identifying specific pollutant mixtures, our study highlighted exposome variations in SGA neonates. Notably, most SGA neonates were born to smoking mothers, reinforcing previous evidence linking smoking to SGA (Govarts et al., 2016; Ishitsuka et al., 2024). However, our network and correlation analyses revealed how maternal smoking could alter pollutant interactions in these neonates.

In smoking mothers, a new pollutant cluster emerged, combining PAHs, OCPs, low-chlorinated PCBs, and Pb (Sequí-Canet et al., 2022). This smoking-associated mixture is likely a major driver of intrauterine growth restriction due to the following mechanisms:

- OCPs impair the insulin-like growth factor (IGF) system, which is critical for fetal growth regulation (Boada et al., 2007; Yesildemir and Celik, 2024).
- PCBs, particularly low-chlorinated congeners, disrupt testosterone and luteinizing hormone levels, increasing the risk of SGA (Tang et al., 2018). In fact, PCBs have been negatively associated with birth weight in Northern European neonates (Halldorsson et al., 2008).
- PAHs cross the placenta, bind to aromatic hydrocarbon receptors (AhR), and disrupt placental vascularization, restricting oxygen and nutrient transport (Sewor et al., 2024).

Compounding these effects, synergistic, additive, and antagonistic interactions between pollutants may modify the biological impact of this smoking-related mixture. Supporting this, SGA neonates exhibited stronger correlations between toxic metals, OCPs, and PAHs compared to AGA and LGA neonates.

4.2. Implications for precision public health

This study provides a comprehensive exposome characterization in neonates from an isolated, non-urban environment. The complexity of exposure profiles suggests that focusing on individual pollutants may be insufficient; instead, multi-component risk assessment is required.

Nevertheless, our findings reinforce the role of smoking as a key environmental factor driving adverse perinatal outcomes. Beyond confirming the association between smoking and SGA, our study elucidates the specific pollutant mixtures linked to maternal smoking. These insights underscore the need for targeted public health interventions to reduce tobacco exposure during pregnancy.

Although this is an initial report on the correlation profile of the neonatal exposome, further exposome-wide association studies (ExWAS) are necessary to characterize multi-pollutant exposures and their health implications. Future research should focus on identifying high-risk subpopulations to develop precision-based public health strategies, ultimately mitigating the adverse health impacts of environmental exposures in vulnerable neonates.

5. Strength and limitations

This study is among the first to systematically characterize 106 chemical exposures with diverse physicochemical and toxicological properties in a perinatal setting. The analysis encompasses both persistent lipophilic and non-persistent hydrophilic chemicals, providing a comprehensive assessment of neonatal exposure patterns.

However, several limitations must be acknowledged. One key constraint is the inability to assess all potential environmental toxicants. While our study includes a broad spectrum of organic, inorganic, persistent, non-persistent, classical, and emerging pollutants, it does not evaluate other contaminants that potentially influence SGA. Given the complexity of the external exposome, achieving 100% characterization is practically unfeasible.

Another limitation in our study is the absence of an evaluation of epigenetic regulation in relation to the pollutants involved, mainly because epigenetic mechanisms are among the most likely to account for long-term effects (Dutta and Ruden, 2024), and these effects are particularly challenging for public health policies.

Additionally, some maternal characteristics that could influence pollutant burden were not recorded, including detailed dietary intake and occupational exposures. These factors may contribute to individual variability in exposure levels and warrant further investigation.

Another limitation is the lack of genetic analysis, particularly concerning gene-environment interactions. Given that common genetic polymorphisms modulate the adverse health effects of maternal smoking during pregnancy (Kobayashi et al., 2022), future epidemiological studies should explore potential genetic susceptibility to environmental pollutants.

Despite these limitations, the findings of this study provide novel insights and offer valuable evidence for public health authorities to develop targeted policies aimed at modifying the unfavorable neonatal exposome observed in this population.

6. Conclusion

This study characterizes the external exposome in a non-urban perinatal population, revealing pollutant mixtures that diverge from conventional classifications. Biomonitoring, correlation analyses, and network visualization identified distinct clusters, underscoring the complexity of neonatal exposures and the need for data-driven approaches in environmental health. A strong association between PAHs, OCPs, low-chlorinated PCBs, and Pb—particularly in SGA neonates from smoking mothers—points to co-exposure and additive effects that impair growth and neurodevelopment. The emergence of clusters including rare earth elements and electronic waste-related metals highlights a novel exposure pathway with potential long-term risks. Exposome research thus provides critical insights into real-life mixtures, supporting Precision Public Health by identifying modifiable drivers of disease and informing targeted, evidence-based interventions.

CRediT authorship contribution statement

Ángelo Santana del Pino: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **María Del Pino Quintana-Montesdeoca:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Katherine Simbaña-Rivera:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Data curation. **Manuel Zumbado:** Writing – review & editing, Writing – original draft, Resources, Funding acquisition, Formal analysis, Data curation. **Octavio P. Luzardo:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation. **Luis Alberto Henríquez-Hernández:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation. **Raúl Cabrera-Rodríguez:** Writing – review & editing, Writing – original draft, Data curation. **Maira del Pino Almeida-González:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis. **Luis D. Boada:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2026.114761.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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