



Full length article

Breastfeeding duration and residential setting in relation to childhood exposure to organochlorine pesticides and PCBs: a longitudinal study of the Rhea cohort in Crete

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ABSTRACT

Despite decades-old bans, persistent organic pollutants (POPs), including organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), remain a public health concern owing to persistence and bioaccumulation. Previous Rhea mother–child cohort analyses (Crete, Greece) reported notably high DDE (DDT’s main metabolite) in children, raising questions about postnatal pathways sustaining this post-ban burden. We aimed to characterise associations of residential setting, breastfeeding duration and childhood diet with children’s serum OCP and PCB concentrations, accounting for maternal prenatal serum concentrations. Using linear mixed-effects models, we related breastfeeding duration and residential setting to 947 serum measurements from 443 Rhea children at ages 4, 6.5 and 11 years ($n = 375, 239$ and 333 , respectively). Breastfeeding duration showed the strongest associations, with >4 months (versus never) consistently associated with higher DDE+DDT sum, HCB and PCB concentrations. Associations were strongest at age 4, then attenuated, consistent with growth dilution and elimination, but remained statistically detectable for DDE+DDT sum to age 11, independent of recent diet and parental agricultural occupation. Breastfeeding duration associations were stronger at higher maternal prenatal HCB concentrations (borderline for PCBs), consistent with lactation as one route of maternal-to-child transfer of accumulated body burden. Contrary to the hypothesis that agricultural proximity drives exposure, urban versus rural Heraklion residence was not significantly associated with serum POPs after adjustment for maternal prenatal concentrations, diet and household characteristics. Rather than implying any change to breastfeeding practice, these findings support reducing POP body burden in reproductive-age women, particularly before conception, during pregnancy and lactation, through continued exposure monitoring.

1. Introduction

Persistent organic pollutants (POPs) remain a major public health concern despite regulatory bans introduced several decades ago.

Organochlorine pesticides (OCPs), and in particular 4,4'-dichlorodiphenyltrichloroethane (DDT) and its primary metabolite 4,4'-dichlorodiphenyldichloroethylene (p,p'-DDE), are emblematic of this challenge due to their extreme environmental persistence, lipophilicity,

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and bioaccumulative properties (Mrema et al., 2013; WHO, 2012). Although the agricultural use of DDT has been banned in most European countries, including Greece since the 1970s, DDE continues to be routinely detected in human tissues, reflecting historical use, long biological half-lives, and ongoing exposure via contaminated food chains (Bandow et al., 2020; EFSA, 2006). This persistence has also raised concerns about the presence of illegal or counterfeit pesticides within Europe, especially in areas with intensive farming (Europol, 2012, 2023) such as Crete.

Environmental risks take their greatest toll on children: they experience proportionally higher exposure to environmental chemicals relative to their body weight while their detoxification systems are still immature (Costopoulou et al., 2024; Vrijheid, 2014), and adverse exposures during sensitive developmental stages may cause permanent alterations in the structure and function of developing organs (Ahlborg et al., 1995; Handakas et al., 2023; Robinson & Vrijheid, 2015).

An increasing number of studies have demonstrated the impact of exposure to DDT and DDE during key developmental periods with adverse neurodevelopment, metabolism, and immune function (Hernández-Mariano et al., 2022; Huq et al., 2020; Kyriklaki et al., 2016).

Within this context, the Rhea mother–child cohort in Crete (Greece) provides a unique platform for investigating early-life exposure to POPs. Rhea is the longest-running prospective population-based birth cohort in Greece and has contributed substantially to the European exposome literature, including through its participation in the Human Early-Life Exposome (HELIX) project (Chatzi et al., 2017; Maitre et al., 2018; Vrijheid, 2014). Participants are residents in the prefecture of Heraklion, encompassing both urban and rural populations within a Mediterranean setting characterised by intensive agricultural activity and potentially elevated pesticide exposure. Initial analysis, in the frame of HELIX project (Haug et al., 2018; Jedynak et al., 2021; Tamayo-Uria et al., 2019), revealed notably elevated concentrations of chlorinated chemicals in Rhea and the highest DDE levels for both pregnant women and their children (168 ng/g and 60.1 ng/g serum lipid for the pregnant mothers and their children respectively) among six European cohorts (Haug et al., 2018). Further, follow-up, detailed characterisation using biomonitoring data for DDT, DDE, hexachlorobenzene (HCB) and a wide array of PCB congeners, collected longitudinally across childhood, confirmed elevated exposure to DDT/DDE in Greek children, and detectable levels of most PCBs (Costopoulou et al., 2024). In 947 serum samples from children aged 4–11 years, we previously reported that DDE was the most abundant OCP detected in serum, with concentrations substantially higher than those reported in comparable European cohorts. Median lipid-normalised DDE concentrations were highest in younger children, consistent with early-life exposure followed by gradual elimination and growth dilution. Importantly, the DDT/DDE ratio was consistently below unity across almost all participants, strongly indicating historical rather than recent DDT use, with ongoing exposure likely mediated through maternal transfer (placental transfer during pregnancy and lactational transfer through breast milk after birth) and diet. Furthermore, DDT/DDE sources had been apportioned together with PCBs, indicating common sources. The persistence of these elevated DDE levels and the accompanying PCB levels raise important questions regarding the dominant exposure pathways sustaining this burden.

Several non-mutually exclusive pathways contribute to the sustained exposure of children to lipophilic POPs. Among these, breastfeeding is a potential primary route; OCPs and PCBs readily partition into breast milk, with duration of breastfeeding associated with higher serum concentrations in pediatric populations (Bouwman et al., 2012; Garí et al., 2019; Skrbic et al., 2010; Zamaratskaia et al., 2022). Placental and lactational transfer both depend on the mother's body burden, which reflects her cumulative exposure to these persistent compounds (Mrema et al., 2013). In the Spanish INMA cohort, maternal serum concentrations in early pregnancy, together with breastfeeding, explained

65–93% of the variance in organochlorine concentrations in 4-year-old children (Garí et al., 2019), and toxicokinetic models based on maternal levels and breastfeeding duration can predict children's blood POP levels up to 45 months of age (Verner et al., 2013). Associations with breastfeeding therefore need to be examined after accounting for maternal prenatal serum concentrations, which also make it possible to explore whether the association varies with the mother's concentration. The detailed information on the prevalence and duration of breastfeeding available in the Rhea cohort (Leventakou et al., 2015), together with maternal serum concentrations measured in early pregnancy, allows both questions to be addressed.

Beyond infancy, children's exposure is further modulated by the local environment. In Crete, a region characterised by a strong agricultural profile, persistent residues of DDT and DDE have been reported in agricultural soils (Tsiantas et al., 2023) and in atmospheric samples (Iakovides et al., 2021), along with their compositional profiles. These works indicate that these pollutants do not have localised environmental sources in Crete and originate from historical applications rather than recent use (Iakovides et al., 2021; Tsiantas et al., 2023). While diet (Weitekamp et al., 2021; Yu et al., 2012, (EFSA), 2006) and parental occupation (Coronado et al., 2006) are known contributors to the “take-home” exposure of family members, these pathways are often dictated by geospatial factors. Differences between rural and urban environments may reflect varying proximity to historically treated agricultural land or distinct local dietary sources. However, the extent to which geographic location and specific maternal factors, such as breastfeeding, determine the internal dose of POPs in Greek children remains insufficiently characterised.

Addressing these knowledge gaps is essential for informing the development of effective public health interventions. This follow-up study aims to characterise childhood exposure to organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) in the Rhea cohort, focusing on the following objectives:

- (i) To investigate the association between residential setting (urban vs. rural) and childhood OCP and PCB concentrations.
- (ii) To examine the association between breastfeeding duration and childhood OCP and PCB concentrations, accounting for maternal prenatal serum concentrations, and to assess how this association varies with age during childhood.
- (iii) To investigate whether the association between breastfeeding duration and childhood OCP and PCB concentrations differs according to maternal prenatal serum concentrations.

2. Materials and methods

2.1. Study population

The Rhea study is a population-based birth cohort established in the Prefecture of Heraklion, Crete, Greece. Between February 2007 and January 2008, 1,610 pregnant women were recruited, mostly before 15 weeks of gestation (Chatzi et al., 2017). Eligibility criteria included being older than 16 years and having sufficient proficiency in Greek to understand the study information and procedures. Follow-up assessments were conducted at 24 weeks of gestation, at birth ($n = 1,363$), and when the children were 9 months ($n = 1,222$), 18 months (subproject, $n = 586$), 4 years ($n = 879$), 6.5 years ($n = 626$), 11 years ($n = 350$), and 15 years of age ($n = 420$) (Mouatsou et al., 2025).

The study was conducted in accordance with the principles of the Declaration of Helsinki. At baseline, the study protocol was approved by the Ethics Committee of the University Hospital of Heraklion (reference number: 96/06.02.2007), with subsequent approval from the Research Ethics Committee of the University of Crete. All participants and/or their caregivers provided written informed consent after receiving a detailed explanation of the study procedures.

For the present analysis, concentrations of persistent organic

pollutants (POPs) were available for assessments conducted when the children were approximately 4 years ($n = 375$), 6.5 years ($n = 239$), and 11 years of age ($n = 333$) (Costopoulou et al., 2024). These measurements comprised 947 observations from 443 children. All available repeated measurements were included in the primary mixed-effects analysis to account for the longitudinal structure of the data. As a sensitivity analysis, a complementary analysis was conducted using only the earliest available POP measurement for each child among those with breastfeeding data ($n = 427$). The study design and participant selection are summarised in Fig. S1 (Supplementary material).

2.2. Assessment of exposure to persistent organic pollutants in children and during pregnancy

Blood serum samples were collected during routine well-child visits at the University Hospital of Heraklion, the Heraklion Primary Health Center, or the nearest health center for families residing in rural areas, following standard operating procedures. Samples were stored at -80°C until analysis. Serum concentrations of OCPs and PCBs were measured using gas chromatography–high resolution mass spectrometry (GC-HRMS). The target analytes included the pesticide p,p'-DDT, its metabolite p,p'-DDE, hexachlorobenzene (HCB), and several PCB congeners (28, 52, 101, 105, 114, 118, 123, 138, 153, 156, 157, 167, 180 & 189). Pollutant concentrations were lipid standardised using serum triglycerides and cholesterol concentrations measured in the same sample. The analytical procedure (sample preparation, extraction, cleanup and GC-MS analysis) has been described in detail previously (Costopoulou et al., 2024). Maternal serum levels of DDT, DDE, HCB and selected PCBs (118, 138, 153, 156, and 180) were measured in samples collected at the first prenatal visit, around the 3rd–4th month of pregnancy with a similar method (Vafeiadi et al., 2014). Concentration levels were also lipid normalised. Hereafter, we refer to these as maternal prenatal serum concentrations and use them as a biomarker of the mother's body burden during pregnancy. Indicator PCBs (ind-PCBs) were defined as the sum of congeners 118, 138, 153, 156, and 180 (Costopoulou et al., 2024).

2.3. Breastfeeding

Information on infant breastfeeding practices was obtained from questionnaires administered at the 6-month and 18-month follow-ups, conducted either by telephone or through face-to-face interviews.

The following exposure variables were used to examine potential dose–response associations between breastfeeding and serum concentrations of POPs: (1) breastfeeding duration, categorised as never breastfed, <4 months, ≥ 4 months; and (2) a lactation score categorised as never breastfed, $<\text{median}$, $\geq\text{median}$ (excluding 0 from median), which combines duration and exclusivity of breastfeeding during the first 6 months of life, thereby providing an additional dimension for assessing the dose–response relationship beyond breastfeeding duration alone (Vassilaki et al., 2014). The lactation score was derived from detailed monthly feeding data. For each month, a value was assigned as follows: 0 for no breastfeeding, 1 for complementary breastfeeding, and 2 for exclusive or predominant breastfeeding (fully breastfed). The resulting score ranged from 0 to 12 and may provide greater explanatory power than breastfeeding duration alone (Krause et al., 2010).

The 4-month cut-off was chosen because this is also the earliest age at which complementary foods may be introduced according to European recommendations (Fewtrell et al., 2017). Thus, the >4 months category captures breastfeeding that continued into the complementary-feeding period. The cut-off also provided comparison groups of adequate size (Table 1).

2.4. Residential setting

Detailed residential histories were obtained from the Rhea cohort,

Table 1

Breastfeeding profile in Rhea children. Continuous variables are reported as mean (standard deviation, SD), median, and min-max; categorical variables are presented as frequency counts and percentages [n (%)].

	No breastfeeding (N=51)	$\leq 4\text{m}$ (N=233)	$> 4\text{m}$ (N=143)	Overall (N=427)
Age (yrs)				
Mean (SD)	5.1 (2.1)	4.8 (1.5)	5.1 (1.9)	4.9 (1.8)
Median [Min, Max]	4.2 [4.0, 12.0]	4.2 [4.0, 11.8]	4.2 [4.0, 11.5]	4.2 [4.0, 12.0]
Gender				
Male	27 (52.9%)	136 (58.4%)	84 (58.7%)	247 (57.8%)
Female	24 (47.1%)	97 (41.6%)	59 (41.3%)	180 (42.2%)
Maternal age at delivery (yrs)				
Mean (SD)	31.2 (5.4)	29.8 (4.7)	30.9 (4.2)	30.4 (4.6)
Median [Min, Max]	30.0 [19.0, 43.0]	30.0 [19.0, 44.0]	31.0 [17.0, 42.0]	30.0 [17.0, 44.0]
Missing	0 (0.0%)	2 (0.9%)	0 (0.0%)	2 (0.5%)
Maternal education				
Low	9 (17.6%)	35 (15.0%)	9 (6.3%)	53 (12.4%)
Medium	30 (58.8%)	128 (54.9%)	55 (38.5%)	213 (49.9%)
High	10 (19.6%)	66 (28.3%)	75 (52.4%)	151 (35.4%)
Missing	2 (3.9%)	4 (1.7%)	4 (2.8%)	10 (2.3%)
Passive smoker				
No	16 (31.4%)	84 (36.1%)	77 (53.8%)	177 (41.5%)
Yes	32 (62.7%)	137 (58.8%)	57 (39.9%)	226 (52.9%)
Missing	3 (5.9%)	12 (5.2%)	9 (6.3%)	24 (5.6%)
Ethnicity				
Greek	48 (94.1%)	224 (96.1%)	137 (95.8%)	409 (95.8%)
Other	2 (3.9%)	8 (3.4%)	6 (4.2%)	16 (3.7%)
Missing	1 (2.0%)	1 (0.4%)	0 (0.0%)	2 (0.5%)
Residence area				
Rural	21 (41.2%)	103 (44.2%)	45 (31.5%)	169 (39.6%)
Urban	24 (47.1%)	103 (44.2%)	85 (59.4%)	212 (49.6%)
Missing	6 (11.8%)	27 (11.6%)	13 (9.1%)	46 (10.8%)
Geographic group (Urban / Group 1–3)				
Urban	24 (47.1%)	103 (44.2%)	84 (58.7%)	211 (49.4%)
Group 1 (Rural North)	4 (7.8%)	42 (18.0%)	22 (15.4%)	68 (15.9%)
Group 2 (Rural Central)	9 (17.6%)	28 (12.0%)	17 (11.9%)	54 (12.6%)
Group 3 (Rural South)	8 (15.7%)	33 (14.2%)	7 (4.9%)	48 (11.2%)
Missing	6 (11.8%)	27 (11.6%)	13 (9.1%)	46 (10.8%)
Parity				
Multiparous	34 (66.7%)	130 (55.8%)	78 (54.5%)	242 (56.7%)
Primiparous	17 (33.3%)	102 (43.8%)	65 (45.5%)	184 (43.1%)
Missing	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Pre-pregnancy BMI kg/m^2				
Mean (SD)	27.1 (6.2)	24.9 (4.7)	24.0 (4.5)	24.9 (4.9)
Median [Min, Max]	24.9 [17.6, 44.9]	23.9 [15.2, 46.9]	22.9 [18.1, 44.9]	23.6 [15.2, 46.9]
Missing	1 (2.0%)	4 (1.7%)	5 (3.5%)	10 (2.3%)
Smoking status				
Non-smokers	29 (56.9%)	132 (56.7%)	110 (76.9%)	271 (63.5%)
Quit during pregnancy	8 (15.7%)	44 (18.9%)	14 (9.8%)	66 (15.5%)
Smokers during pregnancy	11 (21.6%)	49 (21.0%)	15 (10.5%)	75 (17.6%)
Missing	3 (5.9%)	8 (3.4%)	4 (2.8%)	15 (3.5%)

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Table 1 (continued)

	No breastfeeding (N=51)	≤ 4m (N=233)	> 4m (N=143)	Overall (N=427)
Smoking status during pregnancy				
During pregnancy smokers	12 (23.5%)	58 (24.9%)	15 (10.5%)	85 (19.9%)
Early pregnancy smokers	6 (11.8%)	28 (12.0%)	12 (8.4%)	46 (10.8%)
Non-smokers	29 (56.9%)	132 (56.7%)	109 (76.2%)	270 (63.2%)
Missing	4 (7.8%)	15 (6.4%)	7 (4.9%)	26 (6.1%)
Gestational age				
Mean (SD)	38.0 (1.2)	38.1 (1.5)	38.3 (1.7)	38.1 (1.5)
Median [Min, Max]	38.0 [35.0, 40.0]	38.0 [32.0, 41.0]	38.0 [31.0, 41.0]	38.0 [31.0, 41.0]
Missing	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Birth weight				
Mean (SD)	3.12 (0.39)	3.12 (0.45)	3.25 (0.51)	3.16 (0.47)
Median [Min, Max]	3.14 [2.16, 4.00]	3.12 [1.86, 4.25]	3.27 [1.13, 4.35]	3.17 [1.13, 4.35]
Missing	0 (0.0%)	2 (0.9%)	1 (0.7%)	3 (0.7%)
Lactation score				
No breastfeeding	51 (100.0%)	0 (0.0%)	0 (0.0%)	51 (11.9%)
≤ median	0 (0.0%)	188 (80.7%)	0 (0.0%)	188 (44.0%)
> median	0 (0.0%)	32 (13.7%)	134 (93.7%)	166 (38.9%)
Missing	0 (0.0%)	13 (5.6%)	9 (6.3%)	22 (5.2%)
Breastfeeding				
Never	51 (100.0%)	0 (0.0%)	0 (0.0%)	51 (11.9%)
Ever	0 (0.0%)	233 (100.0%)	143 (100.0%)	376 (88.1%)

including residential moves and end-of-residence dates, covering the period from pregnancy to the age at pollutant assessment. Bio-monitoring observations were retained only when the child's residential location (i.e., reported address and/or municipal unit) at the time of sample collection could be confidently identified. Among children with a single recorded residential location, 608 observations met this criterion. Nine observations were excluded due to missing information. Some children had multiple recorded residential locations. Observations from children who moved within the same municipal unit were retained ($n = 177$). For children who moved between municipal units, observations were retained only when their residential location at the time of sampling could be clearly established and sampling had occurred before the first change in municipal unit ($n = 15$). All remaining observations were excluded to minimise the risk of spatial misclassification. The final dataset comprised 800 observations with clearly defined residential contexts. Residential location at the time of sampling was dichotomised as urban (the metropolitan area of Heraklion) or rural (all other municipal units within the county, which are predominantly rural).

To evaluate residential context at the resolution supported by the data, participants were classified into four mutually exclusive groups: the urban municipality of Heraklion ($n=211$ children) and three geographically defined rural zones of Heraklion prefecture: i) Rural North (intensive banana greenhouse production and peri-urban mixed cultivation; $n=68$), ii) Rural Central (predominantly viticulture and olive groves around the Archanes–Peza basin; $n=54$), and iii) Rural South (Messara Plain horticulture, greenhouses, and olive groves; $n=48$) (Fig. S2; Supplementary material). The 61 rural municipal units contributing data had a median of 2 participants per unit (range 1–34), precluding analysis at finer spatial resolution. The binary urban-versus-rural contrast was retained as the primary residential exposure variable; the four-zone classification was evaluated as a planned secondary analysis to characterise heterogeneity within the rural component. Municipality-level percentages of land use types, including vineyards and olive-groves, derived from CORINE Land Cover 2006 dataset (Copernicus Land Monitoring Service, 2020) and linked to participants based on their municipality of residence were further evaluated in

sensitivity analyses (Table S9; Supplementary material).

2.5. Other variables

We considered the following minimal set of potential confounders in our models, based on a Directed Acyclic Graph (DAG) (Fig. S3; Supplementary material). Maternal age at delivery, educational level at recruitment (low: ≤ 9 years, medium: > 9 years up to attending post-secondary school education and high: attending university or having a university/technical college degree), parity (primiparous, multiparous), smoking exposure in the household the 1st year of life (yes, no), pre-pregnancy BMI (kg/m^2 as continuous), maternal Greek ethnicity (yes, no), gestational age (continuous), parental occupation in agriculture, child's diet at age four years (consumption of milk, dairy products, eggs, fatty fish, poultry, red meat, processed meat and meat products) and area of residency (urban - Heraklion city vs rural - Heraklion county) and maternal prenatal serum concentration. Because detailed dietary data were collected only at age 4, this assessment was used for all three time points as an indicator of habitual early-childhood diet. Maternal prenatal serum concentration of the matched pollutant (Section 2.2) had two roles: it was included as a covariate, to account for prenatal exposure and for maternal characteristics related to both breastfeeding and child concentrations (Fig. S3; Supplementary material), and it was examined as a potential modifier of the association between breastfeeding and child serum concentrations (Section 2.6).

2.6. Statistical analysis

Descriptive statistics for continuous variables are reported as mean (SD), median, and range; categorical variables are summarised as frequency counts and percentages (n (%)) (Table 1). Pairwise associations among model covariates were examined to identify potential collinearity using Pearson $|r|$ (continuous–continuous), Cramér's V (categorical–categorical), and the correlation ratio η (mixed pairs); all metrics scaled to $[0,1]$ (Fig. S4; Supplementary material). Spearman rank correlations described the association between maternal prenatal and child serum concentrations (Fig. S5; Supplementary material). Because POP concentrations were right-skewed (Shapiro–Wilk $p < 0.001$), all regression models used log-transformed lipid-adjusted concentrations as outcomes.

To evaluate the association between breastfeeding duration and child body burdens of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), we applied linear mixed-effects models (nlme package, R version 4.4.1). All available repeated measurements per child (ages 4, 6.5, and 11 years) were included; a random intercept per child was specified to account for within-child correlation across time points. Covariates were selected a priori from a directed acyclic graph (Fig. S3; Supplementary material) representing assumed causal relationships among maternal and child characteristics, residential setting, breastfeeding, diet, and pollutant concentrations. The fully adjusted model (Model B2) included child age at sample collection (continuous), sex, birth weight, gestational age, ethnicity, maternal age at delivery, parity, pre-pregnancy BMI, maternal education, parental agricultural occupation, passive smoke exposure in early childhood, dietary intake (milk and dairy products, eggs, fatty fish, poultry, red and processed meat), residential setting (in breastfeeding models), and the matched log-transformed maternal pollutant concentration. The minimally adjusted Model B1 included only age and sex. The six dietary variables (milk and dairy products, eggs, fatty fish, poultry, red meat and processed meat) were retained as separate covariates rather than collapsed into a composite dietary score. The log-transformed maternal concentration was included as an additional covariate in all models to adjust for prenatal exposure transfer. Regression coefficients (β) with 95% confidence intervals (CI) and two-sided p -values are reported throughout. To examine whether the association between breastfeeding and child pollutant levels varied by maternal prenatal serum

concentration, we tested a multiplicative interaction term (breastfeeding group $\times$ log-transformed maternal pollutant concentration) within Model B2 for each outcome with a corresponding maternal measurement. To address multiple comparisons across the six primary associations (three chemicals $\times$ two breastfeeding categories), we applied Benjamini-Hochberg (BH) false discovery rate (FDR) correction within each model separately. To formally assess whether breastfeeding associations differed across age groups, we fitted a pooled linear model across all three assessment waves with a breastfeeding $\times$ age-group interaction term and compared it to the model without the interaction using an F-test (Fig. S17a; Supplementary material).

A principal component analysis (PCA) of the six dietary covariates was conducted as a supplementary analysis to characterise intercorrelations and dietary patterns in the cohort, and to formally justify the individual-dietary variable approach (see Tables S11-13; Supplementary material).

Sensitivity analyses comprised: (i) restriction to each child's earliest available measurement (Section 2.1); (ii) the four-zone residential classification (Section 2.4); (iii) address-level proximity to vineyard and olive-grove parcels; and (iv) effect modification of the breastfeeding-pollutant association by maternal prenatal concentration (Table S3; Supplementary material).

2.7. Data imputation

To handle missing covariate data, multiple imputation by chained equations (MICE) was applied using the mice package (van Buuren and Groothuis-Oudshoorn, 2011) with 40 imputed datasets and 20 iterations. Imputation was performed at child level (one row per child, earliest available time point and then we applied Rubin's rule across all the 40 imputed datasets) (Handakas et al., 2022).

3. Results and discussion

Among the 427 children of the present analysis, 42.2% were female, 49.6% were residing in the city of Heraklion - Greece at the time of birth (or at the time of pollutant characterisation), the majority were of Greek origin (95.7%), 34% were breastfed for 4 months or more (Table 1).

3.1. Residential setting and childhood OCP and PCB concentrations

Contrary to the hypothesis that proximity to intensive agricultural activity is the primary risk factor driving exposure in agricultural zones (due to potential ongoing use of banned pesticides), our findings showed only a modest, unadjusted gradient towards slightly higher serum POP concentrations in children residing in the urban center of Heraklion (Figs. 1&2).

In linear mixed-effects models pooling all follow-ups (Fig. 2), the minimally adjusted model (G1) indicated modestly elevated serum HCB and ind-PCB levels among urban residents. After full adjustment for maternal serum POPs, parity, dietary intake, parental agricultural occupation and socio-demographic covariates (G2), these contrasts were attenuated and did not reach statistical significance for any pollutant group. The attenuation under adjustment suggests that the unadjusted urban-rural gradient largely reflects differences in maternal prenatal serum concentrations, diet and household characteristics between settings rather than residence itself, although residential or agricultural sources may still contribute to children's exposure.

To examine whether the absence of a rural-urban contrast in pooled analyses could be masking a localised exposure focus within the rural areas, we sub-classified rural residence into three geographically distinct groups with intense while differentiated agricultural activity (see Section 2.4) and tested each against the urban reference in fully adjusted mixed-effects models (Fig. S7, Table S7; Supplementary material). None of the three rural sub-groups differed significantly from the urban reference for any pollutant (all $p > 0.05$). For ind-PCBs,

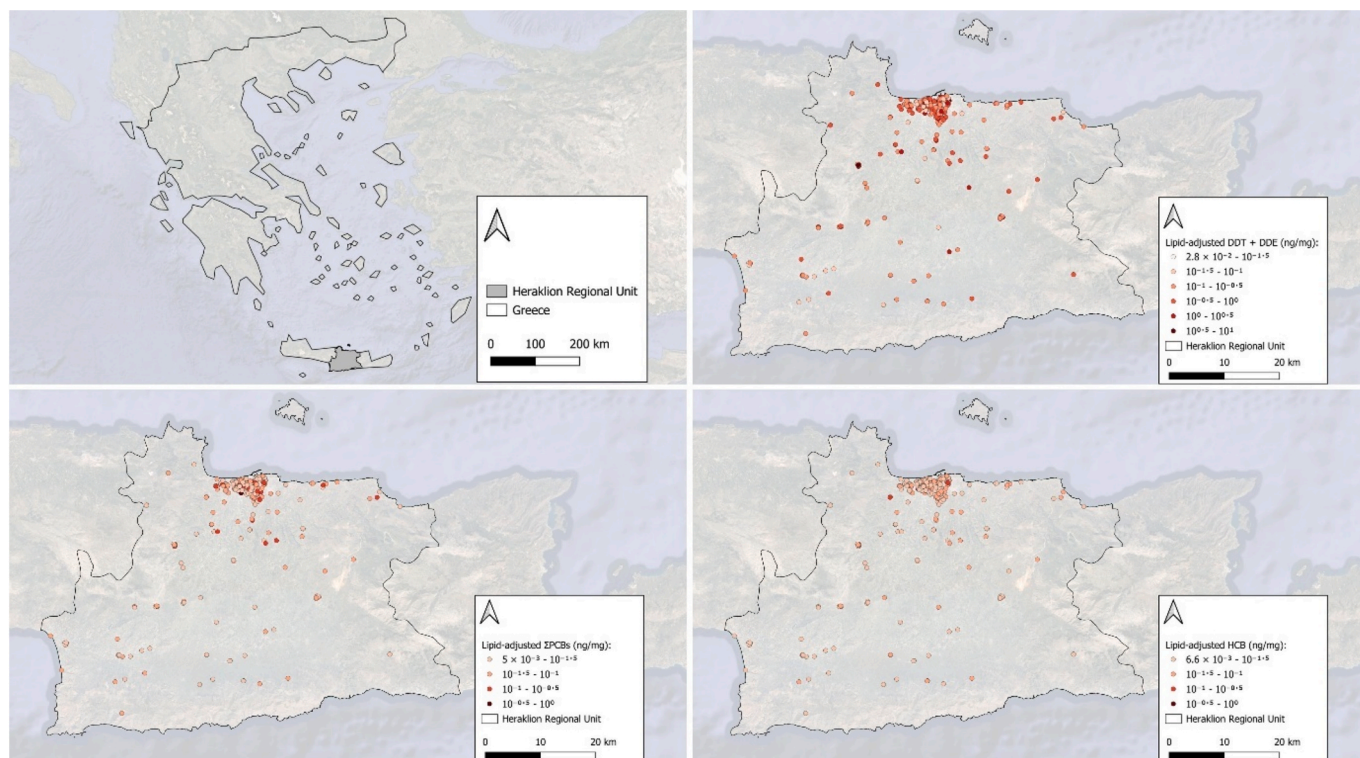


Fig. 1. Geospatial variation in children's serum organochlorine exposure (DDT+DDE sum → top-right panel; ΣPCBs → bottom left panel; HCB → bottom right panel – log-scale) within the Heraklion County, Crete-Greece. General trend for slightly higher levels in the city of Heraklion.

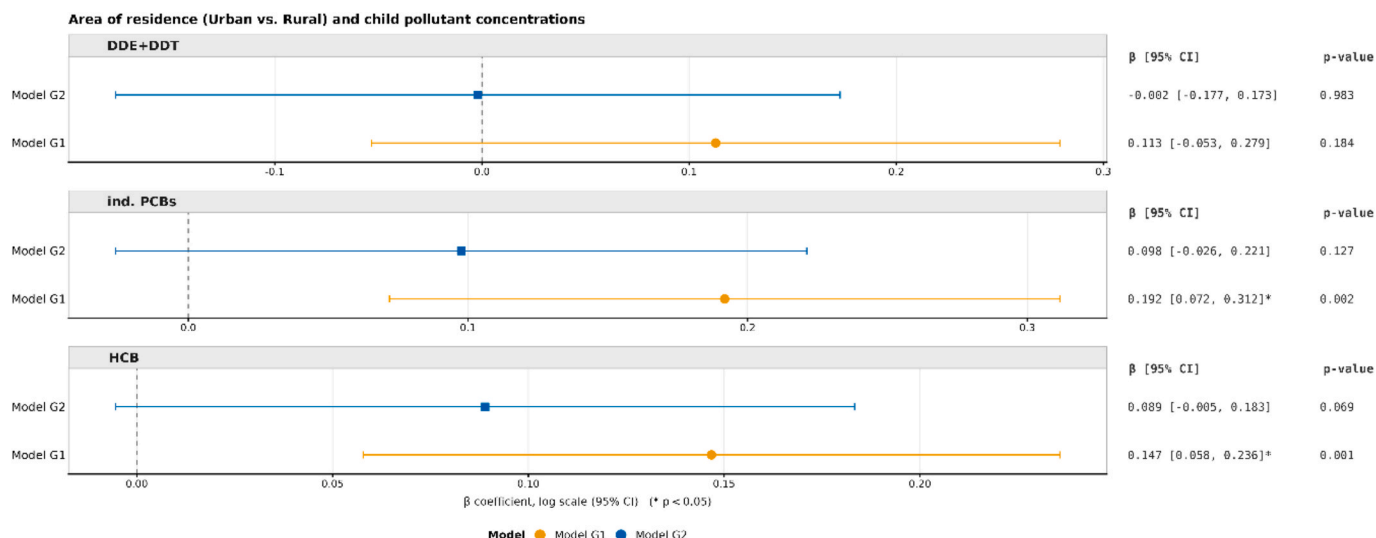


Fig. 2. Adjusted associations between residential setting (urban vs. rural) and child serum concentrations of organochlorine pesticides and indicator polychlorinated biphenyls in the Rhea cohort. Linear mixed-effects regression coefficients (β , log scale) with 95% CIs for the association between urban (reference: rural) residence and log-transformed, lipid-normalised child serum concentrations. Model G1 (orange circles) is the minimally adjusted model, only for maternal prenatal serum concentration levels of OCPs, child age and sex. Model G2 (blue squares) is the fully adjusted model, additionally for birth weight, gestational age, Greek ethnicity, maternal age at delivery, pre-pregnancy BMI, passive smoke exposure in early childhood, maternal education, parity, parental agricultural occupation and child dietary intake.

point estimates were directionally consistent across all three rural groups (Group 1 - North: $\beta = -0.013$, 95% CI -0.178 , 0.153 ; Group 2 - Central: $\beta = -0.130$, 95% CI -0.323 , 0.063 ; Group 3 - South: $\beta = -0.160$, 95% CI -0.362 , 0.042), indicating, if anything, a tendency towards lower rather than higher rural concentrations. Contrasts for DDE+DDT sum and HCB were heterogeneous in sign across groups but uniformly non-significant. These findings provide no evidence for a localised rural exposure focus and are consistent with the pooled urban–rural analysis, which showed no association between residence within Heraklion County and childhood POP concentrations once individual-level covariates were accounted for.

Given the historical use of DDT and structurally related organochlorine compounds in olive and vine cultivation in Crete (Tsiantas et al., 2023), we conducted an additional sensitivity analysis in which community-level proportions of olive groves and vineyards were entered separately into the fully adjusted Model G2, replacing the urban–rural indicator (Fig. S8, Table S8; Supplementary material). Neither land-use variable was significantly associated with the serum sum of DDE and DDT, HCB, or indicator PCBs in children (all $p > 0.35$), and the corresponding point estimates were close to or below the null. These findings provide no evidence of an association between the relative extent of olive groves or vineyards in the surrounding agricultural landscape, where organochlorine compounds have historically been used, and children's body burdens of these pollutants in the present cohort.

To assess whether the pooled null result might mask age-specific contrasts, fully and minimally adjusted area-of-residence models were refitted within each age stratum (Tables S9 & S16; Supplementary material). The pattern was heterogeneous across pollutants, zones and age, with no coherent rural-versus-urban gradient surviving full adjustment at any single time point. In the minimally adjusted models at age 4, children in Rural South (Group 3) showed lower DDE+DDT sum ($\beta = -0.481$, 95% CI -0.784 , -0.179 ; $p = 0.002$) and HCB ($\beta = -0.271$, 95% CI -0.469 , -0.073 ; $p = 0.008$) concentrations relative to the urban reference, and Rural Central (Group 2) showed lower ind-PCBs ($\beta = -0.342$, 95% CI -0.616 , -0.068 ; $p = 0.015$). After adjustment for maternal pollutant concentration, dietary intake and socio-demographic covariates (Model G2), none of these age-4 contrasts remained statistically distinguishable from the null for DDE+DDT sum or HCB. A discordant signal was observed for ind-PCBs at age 4, where Rural North

(Group 1) concentrations were associated with a 29.7% elevation relative to urban after full adjustment ($\beta = +0.260$, 95% CI 0.032 , 0.488 ; $p = 0.026$); the direction of this contrast reversed by age 11 (Rural North vs urban: $\beta = -0.227$, 95% CI -0.401 , -0.053 ; $p = 0.011$). At age 6.5, fully adjusted estimates were null or directionally lower in the rural zones, with statistically detectable reductions for HCB in Rural Central ($\beta = -0.356$, 95% CI -0.636 , -0.075 ; $p = 0.013$) and for ind-PCBs in Rural South ($\beta = -0.667$, 95% CI -1.149 , -0.185 ; $p = 0.007$). Taken together, the age-stratified estimates do not support a consistent direction of contrast between any rural zone and the urban reference, and the unadjusted urban-leaning signals detectable in the youngest stratum were largely accounted for by individual-level maternal, dietary and socio-demographic covariates. These findings are consistent with the pooled longitudinal analysis (Fig. 2) which showed no association between area of residence within Heraklion County and childhood POP concentrations after adjustment for these covariates. Although DDT/DDE residues persist in Cretan soils (Tsiantas et al., 2023) and air (Iakovides et al., 2021), our data provide no evidence that spatial variation in these residues is reflected in children's serum concentrations.

Taken together, the spatial analyses provide no evidence of an association between proximity to agricultural activity and higher childhood POP concentrations. Neither the comparison by area of residence (Fig. 2) nor the finer classification of rural areas, analysed either collectively (Table S7; Supplementary material) or stratified by age (Table S9; Supplementary material), identified a consistent pattern of localised exposure after adjustment for maternal body burden, dietary intake and household characteristics.

The few residual contrasts detectable in the minimally adjusted age-stratified estimates were inconsistent in direction across pollutants and zones and may reflect chance, differences in dietary patterns and household characteristics between settings, or site-specific environmental sources; the present observational design cannot distinguish between these explanations. Contemporary atmospheric measurements in Greece continue to detect organochlorine pesticides (Iakovides et al., 2021) consistent with persistent low-level circulation of these compounds across the broader regional environment. From a public health standpoint, these findings suggest that interventions targeting residential setting alone may have limited effect on childhood POP

concentrations in this population, and that mitigation may need to address food-chain exposures and maternal body burden, which operate across both urban and rural settings.

3.2. Breastfeeding duration and childhood POP concentrations

Ind-PCB concentrations were associated with breastfeeding >4 months ($\beta = 0.580$, 95% CI: 0.410, 0.750; $p < 0.001$) in minimally adjusted Model B1 and $\beta = 0.433$ (95% CI: 0.241, 0.645; $p < 0.001$) in the fully adjusted Model B2, corresponding to a 63% higher child ind-PCB concentration relative to never-breastfed children. The ≤ 4 months category was not significantly associated with child ind-PCBs in either model (Model B1: $\beta = 0.103$, $p = 0.210$; Model B2: $\beta = 0.045$, $p = 0.184$; Table S2).

For HCB, breastfeeding >4 months was associated with $\beta = 0.386$ (95% CI: 0.250, 0.522; $p < 0.001$) in Model B1 and $\beta = 0.272$ (95% CI: 0.140, 0.404; $p < 0.001$) in Model B2, corresponding to a 31% higher child HCB concentration; the ≤ 4 months category was not significantly associated with child HCB in either model (Model B1: $\beta = 0.077$, $p = 0.245$; Model B2: $\beta = 0.028$, $p = 0.694$; Table S2). Longer breastfeeding duration was consistently associated with higher childhood serum OCP and PCB concentrations as has been reported in other cohorts (Andjelkovic et al., 2024; Guerranti et al., 2011; Verner et al., 2013).

For DDE+DDT sum, breastfeeding duration was the factor most strongly associated with childhood concentration levels. In the minimally adjusted mixed-effects model (Model B1, random intercept per child; child age and sex; Fig. 3), children breastfed for >4 months had substantially higher DDE+DDT sum concentrations than non-breastfed children ($\beta = 0.937$, 95% CI: 0.689, 1.185; $p < 0.001$). After full adjustment (Model B2; Fig. 3), the association remained robust ($\beta = 0.821$, 95% CI: 0.549, 1.093; $p < 0.001$), corresponding to a 2.3-fold higher child serum concentration. A weaker association was observed for breastfeeding duration ≤ 4 months versus no breastfeeding, reaching statistical significance in both the minimally adjusted model (Model B1:

$\beta = 0.243$, 95% CI: 0.008, 0.479; $p = 0.043$) and the fully adjusted model (Model B2: $\beta = 0.267$, 95% CI: 0.023, 0.512; $p = 0.036$). This duration-dependent pattern is consistent with a greater cumulative lactational transfer contribution to DDE+DDT sum body burden among children breastfed for longer, within the context of the maternal contaminant burden. After BH-FDR correction across the six primary comparisons, all breastfeeding >4 months vs. never associations remained statistically significant ($p(\text{FDR}) < 0.001$ to 0.001). The breastfeeding ≤ 4 months vs. never association for DDE+DDT did not survive FDR correction (Model B1: $p(\text{FDR}) = 0.064$; Model B2: $p(\text{FDR}) = 0.053$) and should be interpreted with caution (Table S17b; Supplementary material).

The association between breastfeeding for more than four months and the child's serum DDE+DDT sum remained after adjustment for the corresponding maternal prenatal serum concentration. Thus, among children born to mothers with comparable prenatal DDE and DDT concentrations, longer breastfeeding duration was associated with higher childhood serum concentrations of these compounds. However, as neither cord blood nor breast milk concentrations were measured, these analyses cannot distinguish between placental transfer and exposure through breastfeeding. Maternal prenatal concentrations were moderately correlated with child concentrations (e.g. DDE+DDT sum: Spearman's $\rho = 0.41$; $p < 0.001$; Fig. S5), as reported elsewhere (Haug et al., 2018); this correlation may reflect placental transfer, lactational transfer and shared dietary sources (Fig. S5).

Effect modification by matched maternal prenatal pollutant concentration was tested through a multiplicative interaction term (breastfeeding category $\times$ maternal log-pollutant concentration) within the fully adjusted mixed-effects framework (Fig. 4, Table S3; Supplementary material). A statistically significant interaction was detected for HCB ($\beta_{\text{interaction}} = 0.109$, 95% CI: 0.001, 0.216; $p = 0.048$), indicating that the association between breastfeeding and child HCB concentration was stronger among children of mothers with higher prenatal HCB concentrations. For ind-PCBs, the interaction was of comparable magnitude but did not reach the conventional significance

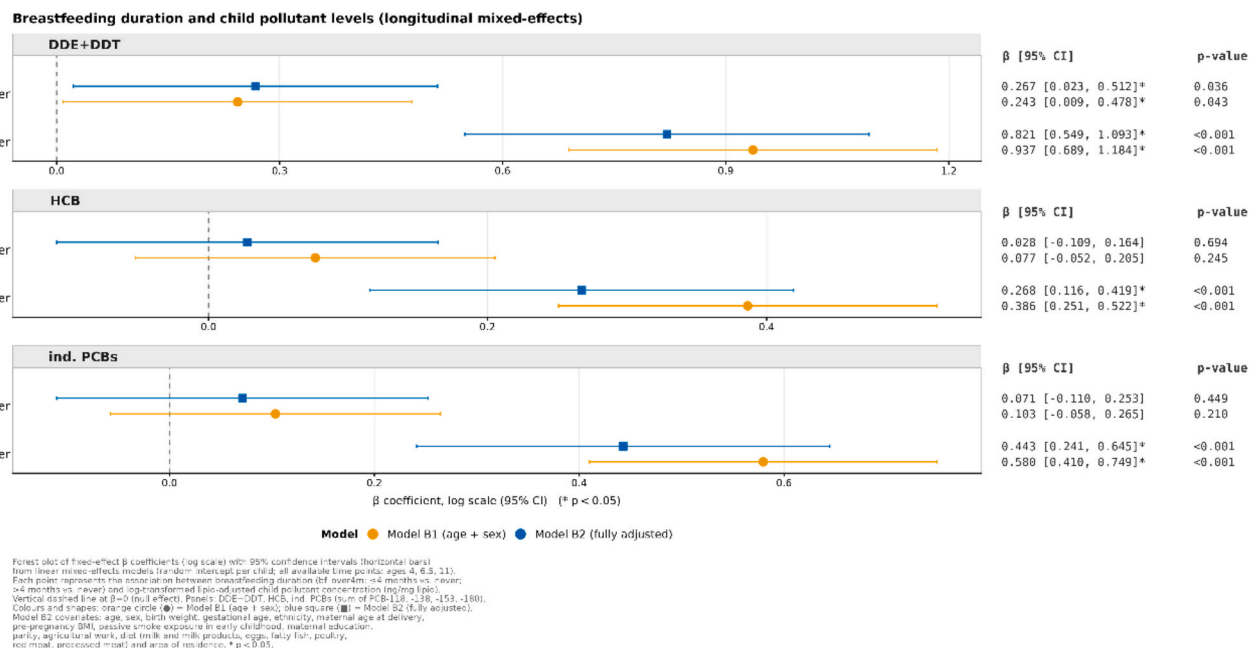


Fig. 3. Linear mixed-effects regression coefficients (β , log scale) with 95% CIs for the association between breastfeeding duration (≤ 4 months vs. never, and > 4 months vs. never) and log-transformed, lipid-normalised child serum concentrations. Model B1 (orange circles) is the minimally adjusted model, adjusted for child age and sex. Model B2 (blue squares) is the fully adjusted model, additionally adjusted for birth weight, gestational age, Greek ethnicity, maternal age at delivery, pre-pregnancy BMI, passive smoke exposure in early childhood, maternal education, parity, parental agricultural occupation, child dietary intake, residential setting, and the matched lipid-normalised maternal prenatal pollutant concentration. β coefficients represent the difference in log-transformed lipid-adjusted child pollutant concentration (ng/mg) associated with each breastfeeding category relative to the never-breastfed reference; positive values indicate higher concentrations among breastfed children.

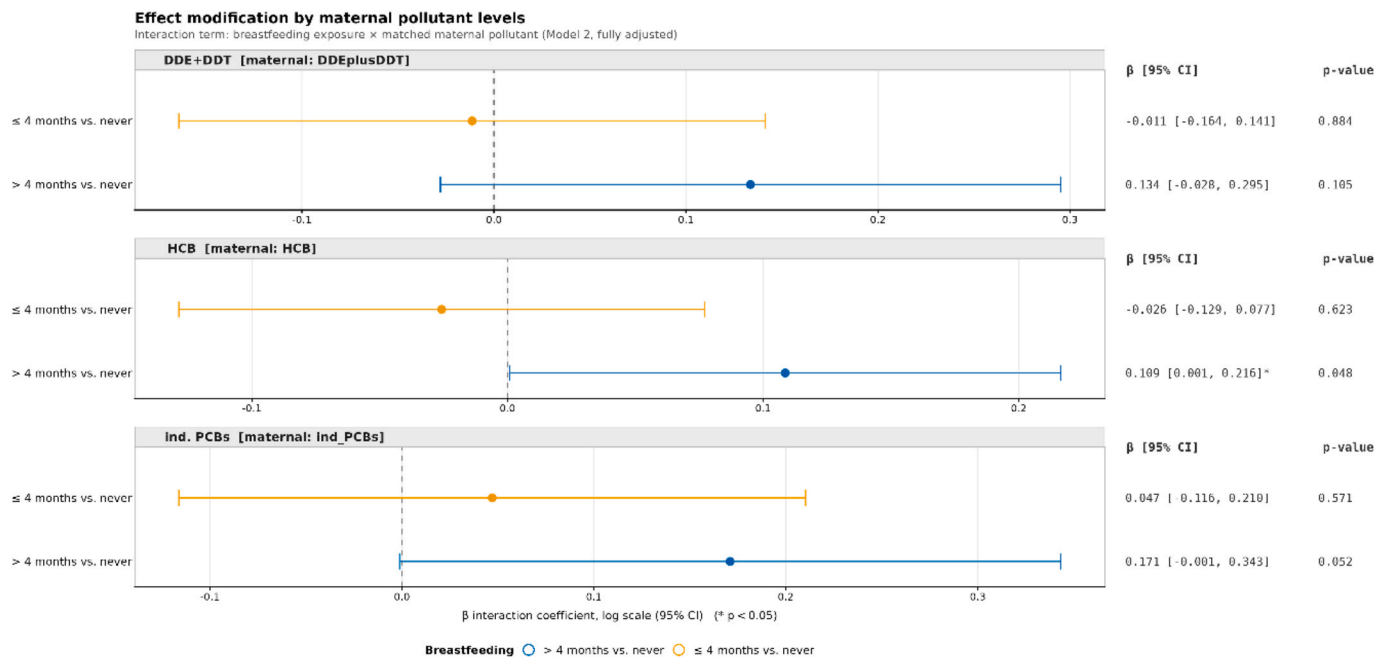


Fig. 4. Multiplicative interaction coefficients ($\beta_{\text{interaction}}$, log scale) with 95% CIs from fully adjusted linear mixed-effects models (Model B2) testing whether the association between breastfeeding duration and child serum pollutant concentration is modified by the matched maternal prenatal pollutant concentration. Positive interaction coefficients indicate that the breastfeeding–child–pollutant association is stronger at higher maternal prenatal pollutant concentrations.

threshold ($\beta_{\text{interaction}} = 0.171$, 95% CI: $-0.001, 0.343$; $p = 0.052$), and for DDE+DDT sum the interaction was non-significant ($\beta_{\text{interaction}} = 0.134$, 95% CI: $-0.028, 0.295$; $p = 0.105$). Taken together, these exploratory findings suggest that the breastfeeding–child–pollutant association may vary with maternal prenatal serum concentration, most clearly for HCB, with a directionally consistent but borderline pattern for ind-PCBs and no detectable modification for DDE+DDT sum; statistical power for interaction terms in cohort studies of this size is, however, limited and these contrasts should be interpreted accordingly. Detailed stratified estimates at the median and 75th percentile of maternal pollutant concentration are reported in [Tables S4 & S5 \(Supplementary material\)](#).

3.3. Parental agricultural occupation, child diet and residential land use

We hypothesised that children from agricultural families, defined by parental employment in agriculture, might experience higher exposures through take-home pathways, such as pesticide residues carried into the home on clothing or in household dust. We observed no association between parental agricultural work and child POP concentrations in the fully adjusted models ([Table S1](#); [Supplementary material](#)). Given that DDT was banned in Greece several decades ago, contemporary occupational exposure to legacy OCPs is likely to be limited, which may explain the absence of an association, and it is consistent with the urban–rural results, presented in [Section 3.1 \(Figs. 1 & 2\)](#). This interpretation was further supported by an address-level sensitivity analysis: residential proximity to vineyards and olive-grove parcels, two cultivation types with distinct historical pesticide profiles, was not associated with child OCP or PCB concentrations ([Fig. S8](#); [Supplementary material](#)). A null association of this kind cannot, however, rule out take-home exposure in individual households.

We further tested whether child diet might explain additional variance in POP concentrations, since food is generally the predominant source of organochlorines after infancy ([Giosuè et al., 2022](#); [Rylander et al., 2009](#)). Among the six food-group variables included in Model B2, egg consumption was the only dietary variable showing a consistent positive association with child POP concentrations, reaching statistical

significance for DDE+DDT sum ($\beta = 0.010$ per g/day, 95% CI: $0.004, 0.016$; $p < 0.001$) and for HCB ($\beta = 0.004$, 95% CI: $0.001, 0.007$; $p = 0.010$), but not for ind-PCBs ([Table S1](#)). No other dietary variable showed a robust association across pollutant groups, and isolated single-pollutant associations of nominal statistical significance observed in either direction for individual food-group/pollutant pairings ([Table S1](#)) were not interpreted as evidence of mechanistic dietary effects in the absence of a coherent cross-pollutant pattern or a plausible biological pathway.

The association between egg consumption and the two groups of legacy organochlorine pesticides, but not indicator PCBs, is consistent with pollutant-specific exposure pathways. DDT, DDE and HCB persist in soils and enter the terrestrial food chain through soil-dwelling invertebrates and surface foraging ([Tsiantas et al., 2023](#)). In Crete, eggs from backyard or small-flock laying hens, common in local production and likely to forage on soils retaining historical pesticide residues, may capture this localised soil-to-food transfer more sensitively than commercial animal products. Ind-PCBs, in contrast, are more strongly influenced by diffuse atmospheric and food-chain sources unrelated to local soil contamination ([Iakovides et al., 2021](#)), which may explain why their association with egg intake was null. The general absence of associations with meat and dairy intake may reflect more homogeneous contamination of these commercial products, limited inter-individual variability in consumption, or both.

3.4. Age-dependent attenuation of the breastfeeding–pollutant association

To assess the robustness of the main findings, a sensitivity analysis was conducted in which the fully adjusted Model B2 was refitted separately within each age stratum (4, 6.5 and 11 years; [Fig. 5](#); [Table S2](#); [Supplementary material](#)). The pattern was pollutant-specific. For DDE+DDT sum, the association between longer breastfeeding (> 4 months) and child serum concentration was strongest at age 4 ($\beta = 1.281$, 95% CI: $0.951, 1.612$; $p < 0.001$; $N = 350$), attenuated by age 6.5 ($\beta = 0.900$, 95% CI: $0.434, 1.365$; $p < 0.001$; $N = 223$) and was further reduced but still detectable by age 11 ($\beta = 0.459$, 95% CI: $0.140, 0.777$; $p = 0.005$; $N = 302$). The shorter-duration contrast (≤ 4 months versus

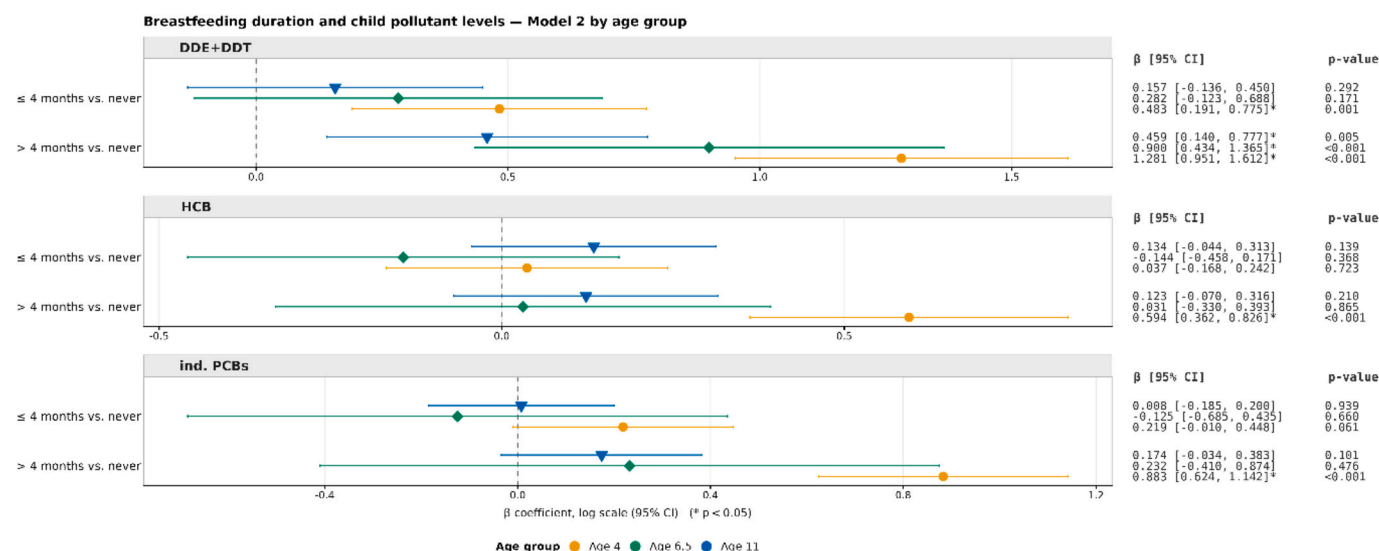


Fig. 5. Age-stratified associations between breastfeeding duration and child POP concentrations in serum. Linear mixed-effects regression coefficients (β , log scale) with 95% confidence intervals for the association between breastfeeding duration and log-transformed, lipid-normalised child serum concentrations. All estimates are derived from the fully adjusted Model B2 and adjusted for child sex, birth weight, gestational age, Greek ethnicity, maternal age at delivery, pre-pregnancy BMI, passive smoke exposure in early childhood, maternal education, parity, parental agricultural occupation, child dietary intake, residential setting (urban/rural), and the matched lipid-normalised maternal prenatal pollutant concentration. β coefficients represent the difference in log-transformed lipid-adjusted child pollutant concentration (ng/mg) associated with each breastfeeding category relative to the never-breastfed reference within the corresponding age stratum; positive values indicate higher concentrations among breastfed children. When fitted within a single age stratum (one observation per child), the random-intercept term is uninformative, and the estimator reduces to ordinary least squares; we retain the mixed-effects specification for consistency with the pooled longitudinal models.

never) reached statistical significance only at age 4 ($\beta = 0.483$, 95% CI: 0.191, 0.775; $p = 0.001$) and was null at the two later time-points.

For HCB and ind-PCBs, the >4-month breastfeeding association was confined to the earliest age stratum: at age 4, both pollutants showed substantial, statistically significant elevations (HCB: $\beta = 0.594$, 95% CI: 0.362, 0.826; $p < 0.001$; ind-PCBs: $\beta = 0.883$, 95% CI: 0.624, 1.142; $p < 0.001$), but at ages 6.5 and 11 the associations were no longer statistically distinguishable from the null (all $p \geq 0.10$). The shorter-duration contrast was non-significant at all three age strata for both pollutants.

These age-stratified patterns are consistent with a scenario in which breastfeeding establishes an early-life body burden that is partially eliminated and diluted by subsequent growth, with the rate of attenuation differing by pollutant. For DDE+DDT sum, the breastfeeding signal persists, albeit attenuated, into pre-adolescence, whereas for HCB and ind-PCBs the signal is detectable only in the youngest stratum and becomes statistically indistinguishable from the null by age 6.5. This pollutant-specific pattern is plausibly explained by differences in lipid solubility, biological half-life and the relative contributions of postnatal versus continued environmental exposure. Our previous analysis of the Rhea cohort's biomonitoring data showed that younger children carried higher lipid-normalised DDE concentrations than older children (Costopoulou et al., 2024), consistent with higher initial burdens followed by elimination and growth dilution; the present age-stratified analyses extend that observation by showing that the association with breastfeeding remains detectable for DDE+DDT sum at age 11. From a toxicological perspective, this suggests that exposures received during the breastfeeding window may contribute to the body burden persisting in pre-adolescence, with implications for assessments of cumulative early-life exposure.

3.5. PCBs and HCB follow a similar pattern

We observed broadly similar patterns for PCBs and HCB as for

DDE+DDT sum in the pooled analyses, with notable congener- and pollutant-specific differences in persistence across childhood. For the sum of ind-PCBs, prolonged breastfeeding (>4 months) was associated with a 56% higher child serum concentration in the fully adjusted Model B2 ($\beta = 0.488$, 95% CI: 0.308, 0.669; $p < 0.001$), consistent with previous reports that PCB levels in infants and young children rise with breastfeeding duration (Andjelkovic et al., 2024; Guerranti et al., 2011; Verner et al., 2013). PCBs share with DDT and DDE high lipophilicity and ready transfer via breast milk, so a parallel lactational signal across both chemical classes is biologically expected.

Within the PCB group, the breastfeeding effect was congener specific. Higher-chlorinated, long-lived congeners showed the strongest associations: PCB-156 ($\beta = 0.876$, $p < 0.001$), PCB-180 ($\beta = 0.849$, $p < 0.001$), PCB-153 ($\beta = 0.817$, $p < 0.001$), PCB-138 ($\beta = 0.737$, $p < 0.001$) and PCB-167 ($\beta = 0.669$, $p < 0.001$) (Fig. 6; Table S1). In contrast, lower-chlorinated congeners, which have shorter biological half-lives and are relatively more influenced by inhalation and ongoing environmental exposure, showed no detectable association with breastfeeding duration (PCB-28: $\beta = -0.068$, $p = 0.540$; PCB-52: $\beta = -0.067$, $p = 0.702$). This congener-specific gradient is biologically plausible: more persistent, lipophilic congeners may accumulate in the mother's body over time and subsequently be transferred to the child during pregnancy and breastfeeding, whereas lower-chlorinated congeners may reflect more diffuse and ongoing environmental exposures. The gradient is nonetheless indirect evidence and cannot apportion exposure between these routes. The age-stratified pattern, however, differed from that of DDE+DDT sum. Whereas the breastfeeding signal for DDE+DDT sum remained statistically detectable into pre-adolescence (Section 3.4), the >4-month association for ind-PCBs was confined to the youngest age stratum (age 4: $\beta = 0.883$, 95% CI: 0.624, 1.142; $p < 0.001$) and was no longer statistically distinguishable from the null at ages 6.5 and 11 (Section 3.4, Table S2; Supplementary material). HCB followed a similar trajectory: prolonged breastfeeding was associated with substantially

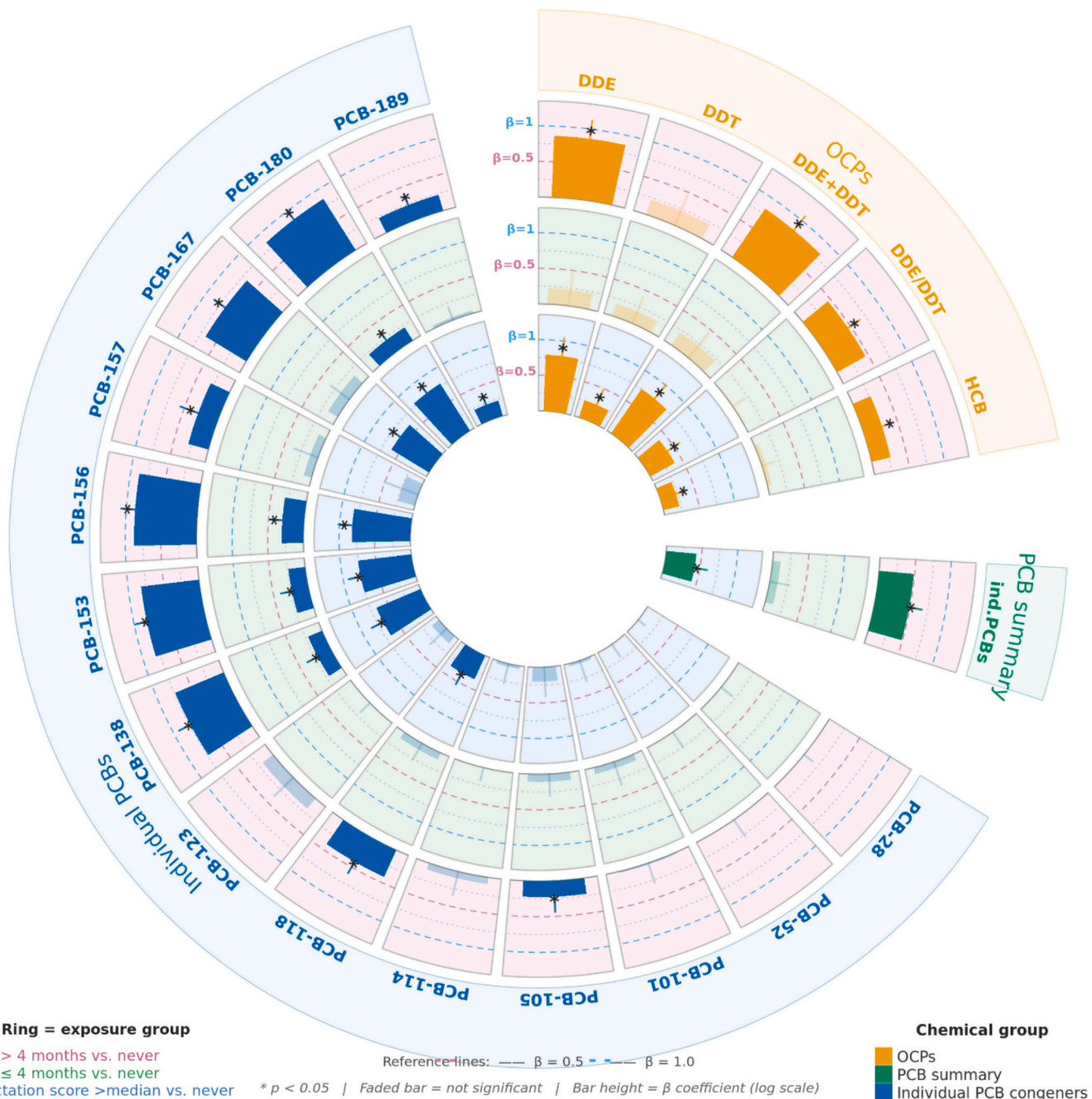


Fig. 6. Circular plot of breastfeeding associations with organochlorine pesticide (OCP) and polychlorinated biphenyl (PCB) concentrations in Rhea children. Each sector of the circle represents one chemical outcome, grouped into three categories: OCPs (DDE, DDT, DDE+DDT sum, DDE/DDT ratio, HCB; orange), PCB summary measure (ind-PCBs; green), and individual PCB congeners (PCB-28, -52, -101, -105, -114, -118, -123, -138, -153, -156, -157, -167, -180, -189; blue). The three concentric rings, each shown on a distinct background, correspond to three breastfeeding exposure contrasts, all relative to never breastfed: outer ring (pink background) - breastfeeding duration >4 months; middle ring (green background) - breastfeeding duration ≤4 months; inner ring (blue background) - extended lactation score above the median. Bar height within each ring represents the regression coefficient (β , log scale) from fully adjusted mixed-effects models (Model B2; random intercept per child). Fully saturated bars indicate statistically significant associations ($p < 0.05$); faded bars indicate non-significant associations. Error bars represent 95% confidence intervals. Dashed reference lines are shown at $\beta = 0.5$ (pink) and $\beta = 1.0$ (blue). All models were adjusted for child age at sample collection, sex, birth weight, gestational age, Greek ethnicity, maternal age at delivery, pre-pregnancy BMI, maternal education, parity, parental agricultural occupation, dietary intake, residential setting (urban/rural), passive smoke exposure in early childhood, and the matched lipid-normalised maternal prenatal pollutant concentration.

higher child serum HCB in the pooled fully adjusted model ($\beta = 0.268$, 95% CI: 0.116, 0.419; $p < 0.001$), and the signal was strongest at age 4 ($\beta = 0.594$, 95% CI: 0.362, 0.826; $p < 0.001$) but did not persist at ages 6.5 or 11 (Table S2; Supplementary material). This faster age-related attenuation of the breastfeeding signal for HCB and PCBs relative to DDE+DDT sum is plausibly explained by differences in postnatal toxicokinetics and the relative balance between an early lactational dose

and continuing low-level environmental input.

Effect modification by maternal prenatal serum concentration was consistent with this pattern. The breastfeeding $\times$ maternal-pollutant interaction term was statistically significant for HCB ($\beta_{\text{interaction}} = 0.109$, 95% CI: 0.001, 0.216; $p = 0.048$; Section 3.2), indicating that the association between breastfeeding and child HCB concentration was stronger among children of mothers with higher prenatal HCB

concentrations. For ind-PCBs the interaction was of comparable magnitude and direction but did not reach the conventional significance threshold ($\beta_{\text{interaction}} = 0.171$, 95% CI: -0.001 , 0.343 ; $p = 0.052$). HCB is highly lipophilic, has a long biological half-life and partitions readily into breast milk and across the placenta (Mrema et al., 2013) which makes greater transfer from mothers with higher concentrations biologically plausible, although the present data cannot isolate placental from lactational transfer.

Taken together, these results suggest that early-life maternal-to-child transfer makes an important contribution to children's concentrations of highly chlorinated PCBs and HCB, with associations with breastfeeding diminishing by mid-childhood. Continuing environmental and dietary exposures sustain the underlying body burden into later childhood but do so independently of breastfeeding history.

3.6. Implications and public health considerations

Collectively, among the factors examined, breastfeeding duration showed the strongest association with legacy organochlorine and PCB concentrations in Rhea cohort children. Spatial environmental factors and parental occupation, which we had hypothesised might generate substantial variability, were not associated with child concentrations once individual-level maternal, dietary and socio-demographic covariates were considered. The persistence of elevated DDE concentrations in this cohort, higher than in many other European child populations, while ind-PCB levels are similar or lower (Costopoulou et al., 2024), is consistent with historical agricultural exposures reaching children through maternal transfer and the food chain, although the present study cannot quantify the contribution of each route. Effect-modification analyses further indicated that the association between breastfeeding and child HCB concentration was stronger among children of mothers with higher prenatal HCB concentrations, with a directionally consistent but borderline pattern for ind-PCBs and no detectable modification for DDE+DDT sum. Breastfeeding confers well-established health benefits for both infants and mothers. In the context of persistent lipophilic pollutants, lactation can also serve as one physiological route of transfer of compounds previously accumulated in the maternal body. The findings of the present study should not be interpreted as a recommendation to curtail breastfeeding; rather, they reinforce the value of reducing women's body burden of these compounds before and during pregnancy, since maternal prenatal serum concentrations ultimately impact what is transferred to the child. In high-exposure settings such as Crete, where DDE concentrations in children remain elevated relative to other European cohorts (Costopoulou et al., 2024), continued biomonitoring of food sources for legacy organochlorine residues may be informative in identifying remaining points of dietary exposure.

This study is subject to several limitations that warrant acknowledgement. First, although the analytic framework leveraged repeated measurements at ages 4, 6.5 and 11 years within a linear mixed-effects model, providing greater statistical power and a more efficient use of the cohort's longitudinal data than would be obtainable from any single cross-section, the observational design cannot establish causality for time-varying determinants such as diet. Reverse causation is implausible for breastfeeding, which is fixed in infancy, but cannot be excluded for diet. Second, breastfeeding duration was based on maternal recall and, while generally reliable in this cohort, may introduce some misclassification, the magnitude and direction of which would tend towards the null. Third, maternal POP concentrations were measured once during pregnancy, and neither cord blood nor breast milk concentrations were available; the analyses therefore cannot separate placental from lactational transfer. Fourth, although we adjusted for a comprehensive set of confounders, residual confounding from unmeasured factors, including indoor environmental exposures, individual differences in xenobiotic metabolism, and finer-grained dietary detail beyond the six food-group variables used here, cannot be excluded. Fifth, the dispersed distribution of rural participants across small municipal units precluded distance-to-

source modelling for individual contamination sources; we addressed this through community-level land-use sensitivity analyses, which were uninformative for any of the three pollutant groups. Sixth, statistical power for the effect-modification analyses is necessarily limited in a cohort of this size, and the borderline interaction estimate for indicator PCBs should be interpreted with corresponding caution. Seventh, detailed dietary information was available only at age 4 years and was used for all three time points, so changes in diet between ages 4 and 11 were not captured; this may have attenuated diet-outcome associations at later ages. Finally, the analytic sample reflects sequential attrition from the original Rhea cohort, and although the retained participants remained broadly representative of the source cohort on key socio-demographic indicators, differential follow-up retention cannot be entirely excluded as a source of selection bias.

Notwithstanding these limitations, confidence in our central inference is supported by the consistency of associations across minimally and fully adjusted models, the coherence of the congener-specific gradient with established toxicokinetic expectations (Section 3.5), and the concordance of our findings with previous biomonitoring analyses in this cohort and the broader literature on mother-to-child transfer of legacy organochlorines. Taken together, these findings indicate that breastfeeding duration, which serves as a marker of the lactational transfer pathway, was the factor most consistently associated with childhood concentrations of legacy OCPs and PCBs.

4. Conclusions

Exposure to legacy organochlorine pesticides and PCBs is widespread within the Rhea cohort. Contrary to the hypothesis that proximity to agricultural land use is a primary determinant of childhood OCP exposure, no coherent rural excess was observed in pooled longitudinal analyses, and the few age- and zone-specific contrasts detectable after adjustment were inconsistent in direction across pollutants and time points; the modest urban-leaning gradient detectable in the youngest age stratum was largely attenuated by adjustment for individual-level covariates and converged to the null by ages 6.5 and 11. This provides no evidence that contemporary agricultural inputs are associated with childhood concentrations, and is compatible with exposure through regionally distributed dietary pathways and maternal transfer. Among the factors evaluated, breastfeeding duration was the strongest correlate of childhood pollutant burden. Longer breastfeeding was consistently and substantially associated with higher childhood serum concentrations of DDE+DDT sum, HCB and ind-PCBs in the fully adjusted longitudinal models. The age-related trajectory of this association was, however, pollutant-specific: the breastfeeding signal for DDE+DDT sum remained statistically detectable into pre-adolescence, whereas the corresponding signal for HCB and ind-PCBs was concentrated in early childhood and no longer detectable by ages 6.5 and 11. Within the PCB group, associations with breastfeeding were strongest for the higher-chlorinated, long-half-life congeners (PCB-138, PCB-153, PCB-180 and related congeners) and were not detected for the shorter-half-life congeners (PCB-28, PCB-52), a pattern that is biologically plausible given the accumulation of the more persistent, lipophilic compounds in the mother's body.

These findings refine the understanding of exposure pathways in the post-DDT era. We found no evidence that contemporary agricultural activity or parental occupation is associated with childhood concentrations in this cohort. Breastfeeding duration, which serves as a marker of the lactational transfer pathway, was consistently associated with them, pointing to maternal body burden, established before and during pregnancy, as a relevant target for prevention. As the Rhea cohort continues into adolescence and adulthood, future analyses will be able to address whether the exposure differences observed between ages 4 and 11 translate into measurable health or developmental outcomes, an open question of considerable importance given the documented endocrine, neurodevelopmental and metabolic toxicity of these compounds.

CRediT authorship contribution statement

Marianna Karachaliou: Writing – original draft, Methodology, Formal analysis. **Evangelos Chandakas:** Writing – original draft, Visualization, Formal analysis, Data curation. **Theodoros Giakoumis:** Writing – original draft, Visualization, Formal analysis. **Alexandra Parada-Torres:** Writing – original draft, Visualization, Formal analysis. **Danae Costopoulou:** Writing – review & editing, Formal analysis. **Leondios Leondiadis:** Writing – review & editing, Formal analysis. **Panu Rantakokko:** . **Hannu Kiviranta:** . **Euripides G. Stephanou:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Antonis Myridakis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2026.110583>.

Data availability

The authors do not have permission to share data.

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