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Prenatal exposure to environmental chemical contaminants and asthma and eczema in school-age children

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Abstract

Background: Emerging evidence suggests that prenatal or early-life exposures to environmental contaminants may contribute to an increased risk of asthma and allergies in children. We aimed to the explore associations of prenatal exposures to a large set of environmental chemical contaminants with asthma and eczema in school-age children.

Methods: We studied 1024 mother–child pairs from Greenland and Ukraine from the INUENDO birth cohort. Data were collected by means of an interview-based questionnaire when the children were 5–9 years of age. Questions from the ISAAC study were used to define asthma, eczema, and wheeze. We applied principal components analysis (PCA) to sixteen contaminants in maternal serum sampled during pregnancy, including perfluoroalkyl substances (PFASs), metabolites of diethylhexyl (DEHP) and diisononyl (DiNP) phthalates, PCB-153, and *p,p′*-DDE. Scores of five principal components (PCs) explaining 70% of the variance were included in multiple logistic regression models.

Results: In a meta-analysis that included both populations, the PC2 score, reflecting exposure to DiNP, was negatively associated with current eczema (OR 0.71, 95% CI 0.52–0.96). Other associations were not consistent between the two populations. In Ukrainian children, the PC3 score (DEHP) was positively associated with current wheeze (adjusted OR 1.56, 95% CI 1.03–2.37), whereas the PC5 score, dominated by perfluorooctanoic acid (PFOA), was inversely associated with current wheeze (OR 0.64, 0.41–0.99). In Greenlandic children, a negative association of PC4 (organochlorines) with ever eczema (OR 0.78, 0.61–0.99) was found.

Conclusions: We found limited evidence to support a link between prenatal exposure to environmental chemical contaminants and childhood asthma and eczema.

It has been well established that intrauterine exposures related to maternal smoking, diet, and microbial agents can influence fetal immune development and contribute to an increased risk of asthma and allergies in children (1, 2). Epidemiological studies suggest that prenatal or early-life exposures to environmental chemical contaminants may also play a role in the development of respiratory and allergic diseases, although the evidence is inconsistent. Mouse and rat models have shown that certain xenobiotic chemicals are able to influence the developing immune system (3, 4). However, the

mechanisms through which these contaminants, such as organochlorines or phthalates, may cause respiratory and allergic conditions in early life remain to be elucidated.

Phthalates are commonly used as plasticizers in building materials, polyvinyl chloride (PVC) floors, food packaging, medical devices, and toys. An increasing number of cross-sectional and case–control studies indicate a link between postnatal phthalate exposures and asthma and allergies (5–10). Thus far, three prospective studies showed that prenatal phthalate exposure may increase the risk of early-onset eczema (11), asthma (12, 13), and respiratory tract infections (12). Prenatal exposures to organochlorine compounds, in particular to persistent legacy pollutants *p,p′*-DDE and PCB-153, have also been associated with asthma, wheezing, and respiratory infections in infancy or early childhood (14–17). A recent meta-analysis of European studies has shown a positive association between DDE and bronchitis or wheeze in early childhood, whereas heterogeneous results were observed for PCB-153 (18). A growing number of epidemiological studies have explored the effect of prenatal exposure to perfluoroalkyl substances (PFASs) on allergic outcomes, with inconsistent results (19–21). PFASs are persistent compounds that are ubiquitously used as surfactants in many applications, such as water- and stain-repellent coatings. No associations were found between maternal perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS) levels and allergies and infectious diseases in Japanese infants at age 18 months (19), but cord blood PFOA and PFOS concentrations were correlated with cord blood IgE levels in Taiwanese newborns (20). Prenatal exposures to PFASs were negatively associated with the development of eczema during the first 24 months, but only in female infants (21).

Thus far, studies reporting associations between environmental chemical contaminants and allergic outcomes examined a single pollutant or a single class of compounds, while other correlated low-level exposures to environmental pollutants were not taken into account. The aim of our study was to explore associations of prenatal exposures to a large set of environmental contaminants, including PFASs, secondary oxidized metabolites of diethylhexyl (DEHP) and diisononyl (DiNP) phthalates, PCB-153, and *p,p′*-DDE, with asthma and eczema symptoms in school-age children from a birth cohort in Greenland and Ukraine. Phthalate exposure is usually determined by measuring the levels of phthalate metabolites in urine. In this study, phthalate exposure was measured in serum, which might be a better estimate of the internal dose than urinary levels. However, concentrations of phthalate monoesters in serum are not reliable measures of exposure, and therefore, we did not investigate phthalate monoesters such as MEHP and MiNP.

Methods

Study population

Between 2002 and 2004, pregnant women from Greenland, Kharkiv (Ukraine), and Warsaw (Poland) were recruited for the INUENDO birth cohort during routine antenatal care visits (22). In total, 567 (85% of eligible) women in Greenland, 612 (25%) women in Ukraine, and 258 (37%) women in Poland were interviewed and provided a blood sample. The follow-up was conducted when the children were between 5 and 9 years old (2010–2012). Participation rates at follow-up were high in Greenland (89%) and in Ukraine (80%), but low in Poland (36%). In this study, we excluded the data from Poland, as the number of mother–child pairs was too low ($n = 92$) to conduct a population-specific analysis. All parents gave written informed consent, and the local ethics committees approved the study.

Questionnaire

Parents were interviewed using a structured questionnaire. In Ukraine, interviews were conducted by pediatricians. In Greenland, the interviews were primarily conducted by a medical doctor, assisted by local health workers. Further details on the follow-up data collection are described elsewhere (23). We studied five health outcomes: ever/current eczema, ever/current wheeze, and ever asthma, based on questions from the standardized International Study of Asthma and Allergies in Childhood (ISAAC) Questionnaire (24, 25). Hay fever was not included, as it was only reported for 0.2% of Ukrainian and 2.9% of Greenlandic children. Potential confounders were also obtained from the questionnaire, except for maternal smoking during pregnancy, which was defined as serum cotinine >10 ng/ml. The other covariates that we included *a priori* were as follows: maternal allergy, maternal education (until the age of ≥18 years *vs* <18 years), maternal age, child sex, child age at follow-up, gestational age at blood sampling, parity (0 *vs* ≥1 previous child births), breastfeeding (>3 months *vs* ≤3 months), and birthweight.

Prenatal exposure to environmental contaminants

Characteristics of the chemical contaminants (e.g., industrial applications, regulatory status, route of exposure) are shown in Table S1. PFASs and phthalates were determined in 100-μl aliquots of serum by liquid chromatography/tandem mass spectrometry, following the same protocol as in Lindh et al. (26) and Specht et al. (27). Quantitative analysis was conducted using a triple quadruple linear ion trap mass spectrometer equipped with a TurboIonSpray source (QTRAP 5500; AB Sciex, Foster City, CA, USA) coupled to a liquid chromatography system (UFLCXR; Shimadzu Corporation, Kyoto, Japan; LC/MS/MS). Secondary oxidized metabolites of DEHP and DiNP were analyzed as follows: mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(hydroxy-iso-nonyl) phthalate (MHiNP), mono-(oxo-iso-nonyl) phthalate (MOiNP), and mono-(carboxy-iso-octyl) phthalate (MCiOP). Analyzed PFASs included perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid

(PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA). PCB-153 and *p,p′*-DDE were analyzed by gas chromatography–mass spectrometry in 2004, as previously described (28). Lipids were determined by enzymatic methods, and lipid adjustment of organochlorines was based on total lipids, calculated as 1.13 + 1.31*(triglycerides + cholesterol) (29). Limits of detection (LODs) ranged from 0.005 to 0.2 ng/ml, and the interassay coefficients of variation in quality control samples (n = 76) were 10–19% (median 15%; Table S2). Data below the LOD (0–24%) were singly imputed from a log-normal probability distribution, accounting for study population and observed values for other contaminants and allowing residual variances to vary by population (30).

Data analysis

In total, 1024 mother–child pairs (Ukraine n = 492, Greenland n = 532) with available maternal sera and data on at least one of the child outcomes available were included in data analyses. Contaminant levels were first log-transformed, and then mean-centered by population, which was applied to eliminate the large differences in central tendencies between the two populations for the exposures (31). Standardized exposures (n = 16) of all 1024 mothers were subjected to a principal component analysis (PCA) with varimax (orthogonal) rotation. PCA is a dimensionality reduction method that transforms a number of possible correlated variables into a smaller number of uncorrelated principal components (PCs). PCA seeks a linear combination of the original observed variables such that the maximum variance is extracted from the variables. The coefficients defining these linear combinations are called 'factor loadings' and are the correlations of the individual contaminants with the components. For each of the retained PCs, standardized PC scores were computed as linear combinations of scoring coefficients and standardized observed variables for each mother–child pair. Because PC scores are uncorrelated, they were tested together in unadjusted and adjusted multiple logistic regression models as explanatory variables, with eczema and asthma symptoms as dependent variables. We used a multiple imputation approach to deal with missing outcomes and covariates (Appendix S1 and Table S3). Logistic regression analyses were performed stratified by population. The overall effect was estimated by combining the population-specific estimates through standard fixed-effects meta-analysis. The three following sensitivity analyses were performed: first, we performed a pooled analysis (adjusted for population); second, we assessed models excluding children aged 5 or 9 years, or children with missing data on age; and third, instead of PC scores, we tested each individual contaminant separately in logistic regression models.

Results

Characteristics of the 492 Ukrainian and 532 Greenlandic mother–child pairs are presented in Table 1. The prevalence of eczema and asthma symptoms was higher in children from Greenland than in Ukrainian children, except for ever eczema (Ukraine: 14.8%, Greenland: 12.3%). The question 'Has your child ever had asthma?' was answered positively by 1.6% in Ukraine *vs* 12.4% in Greenland. Prolonged breastfeeding (more than 3 months) was very common in both populations (Ukraine: 85%, Greenland: 93%), but smoking during pregnancy was also common, especially in Greenland (Ukraine: 15%, Greenland: 56%). Exposure levels of MEHHP, MHiNP, all eight PFASs, and PCB-153 were higher in pregnant women from Greenland than in women from Ukraine, whereas levels of MECPP and *p,p′*-DDE were higher in Ukrainian women. Pearson correlation coefficients of the 16 contaminants ranged from −0.10 to 0.78 (Figure S1).

Results of the PCA are shown in Table 2. The first five components, accounting for 70% of the total variance, were retained as they displayed eigenvalues >1. Six PFAS exposures were found to load (>0.4) on PC1; all DiNP exposures loaded on PC2; all DEHP exposures loaded on PC3; the organochlorines loaded on PC4; and PFOA, PFHpA, and PFOS loaded on PC5.

Table 3 shows unadjusted and adjusted associations of the PC scores for each of the five extracted components with asthma, eczema, and wheeze in children. Adjustment for covariates did not meaningfully change the results. The PC3 score (mainly reflective of DEHP metabolites) was positively associated with current wheeze in Ukrainian children (adjusted OR 1.56, 95% CI 1.03–2.37; P = 0.037), whereas the PC5 score (dominated by PFOA and PFHpA) was inversely associated with current wheeze (OR 0.64, 0.41–0.99; P = 0.046). In children from Greenland, a negative association of PC4 (dominated by organochlorines) with ever eczema (OR 0.78, 0.61–0.99; P = 0.043) was found. In the analysis of both populations combined, only PC2 (DiNP metabolites) was significantly associated with a lower odds of current eczema (adjusted OR 0.71, 0.52–0.96; P = 0.026). Both in Ukraine and Greenland, similar negative associations between PC2 and current eczema were found in boys and girls (P interaction > 0.5). In a pooled analysis, similar odds ratios were obtained. The association between PC2 and current eczema was the only significant finding (OR 0.70, 0.51–0.95; P = 0.023). In the sensitivity analysis restricted to children aged 6–8 years, no differences were observed in children from Ukraine (n = 483). In children from Greenland (n = 427), the inverse association between organochlorines (PC4) and ever wheeze became statistically significant (OR 0.80, 0.66–0.97; P = 0.026); the other associations did not change.

Table S4 presents logistic regression models of all individual contaminants and outcomes (by population and combined). Overall, results were highly consistent with those from the models using PC scores as explanatory variables. In the single-pollutant models, significant inverse associations between the organochlorines and ever wheeze were found in both populations combined (PCB-153: OR 0.84, 0.70–0.99; P = 0.041, *p,p′*-DDE: OR 0.82, 0.70–0.96; P = 0.015). Single DiNP metabolites were all negatively associated with current eczema, but only MCiOP in children

Table 1 Characteristics of 492 Ukrainian and 532 Greenlandic mother–child pairs from the INUENDO birth cohort

Characteristic	Ukraine	Greenland	*P*-value*
N	492	532	
Child characteristics			
Sex, *n* girls (%)	228 (46.6)	241 (45.7)	0.77
Gestational age at blood sampling, weeks, mean ± SD	24 ± 11	25 ± 9	0.05
Age at follow-up, years, mean ± SD	7.1 ± 0.4	8.2 ± 0.6	<0.001
Breastfeeding, more than 3 months, *n* (%)	415 (84.7)	476 (93.3)	<0.001
Birthweight, g, mean ± SD	3270 ± 418	3600 ± 592	<0.001
Child outcomes at follow-up			
Ever eczema, *n* (%)	73 (14.8)	59 (12.3)	0.24
Current eczema, *n* (%)	21 (4.3)	53 (10.2)	<0.001
Ever wheeze, *n* (%)	33 (6.8)	97 (19.4)	<0.001
Current wheeze, *n* (%)	16 (3.3)	27 (5.4)	0.10
Ever asthma, *n* (%)	8 (1.6)	62 (12.4)	<0.001
Maternal characteristics			
Age at blood sampling, years, mean ± SD	25.1 ± 4.8	26.8 ± 6.1	<0.001
Smoking during pregnancy, *n* (%)†	76 (15.5)	298 (56.0)	<0.001
Education until age ≥18 years, *n* (%)	289 (60.3)	240 (49.7)	<0.001
Parity, ≥1, *n* (%)	92 (18.7)	338 (66.7)	<0.001
Maternal allergy	41 (8.4)	64 (16.6)	<0.001
Exposures, GM (p5–p95)			
Diethylhexyl (DEHP) phthalate metabolites, ng/ml			
MEHHP	0.51 (0.11–3.05)	0.71 (0.24–2.38)	<0.001
MEOHP	0.11 (0.03–0.38)	0.12 (0.05–0.29)	0.12
MECPP	1.01 (0.37–3.99)	0.63 (0.25–1.99)	<0.001
Diisononyl (DiNP) phthalate metabolites, ng/ml			
MHiNP	0.04 (0.01–0.44)	0.24 (0.07–0.79)	<0.001
MOiNP	0.02 (0.002–0.22)	0.02 (0.004–0.08)	0.79
MCiOP	0.27 (0.05–4.25)	0.27 (0.07–3.51)	0.77
Perfluoroalkyl substances, ng/ml			
PFHxS	1.53 (0.47–4.12)	2.14 (0.97–5.10)	<0.001
PFHpA	0.03 (0.01–0.13)	0.05 (0.01–0.15)	<0.001
PFOS	4.88 (2.34–9.94)	20.6 (10.2–49.6)	<0.001
PFOA	0.97 (0.45–2.34)	1.79 (0.80–3.66)	<0.001
PFNA	0.62 (0.30–1.38)	0.73 (0.33–2.01)	<0.001
PFDA	0.16 (0.07–0.35)	0.42 (0.16–1.16)	<0.001
PFUnDA	0.16 (0.06–0.52)	0.68 (0.17–2.63)	<0.001
PFDoDA	0.04 (0.02–0.11)	0.13 (0.04–0.40)	<0.001
Organochlorines, ng/g lipids			
PCB-153	25.5 (8.43–64.0)	105 (21.0–528)	<0.001
p,p′-DDE	643 (277–1555)	273 (47.1–1294)	<0.001

*Test for differences between the two populations: *t*-test for means and chi-square test for proportions.
†Defined as serum cotinine >10 ng/ml.

from Greenland showed a significant association (OR 0.71, 0.50–1.00; $P = 0.049$).

Discussion

There is literature to suggest that maternal environmental exposures to pollutants that cross the placental barrier may affect respiratory health and immune function of the developing fetus. In the present study, we found limited evidence to support a link between prenatal exposures to environmental contaminants including PFASs, phthalates (metabolites of DEHP and DiNP), PCB-153, and *p,p′*-DDE with asthma and eczema symptoms in 5- to 9-year-old children from a birth cohort in Greenland and Ukraine. In the analysis of both populations combined, we observed a modest association between the PC score that was dominated by DiNP metabolites and a lower prevalence of current eczema.

We examined data from a relatively large prospective birth cohort that was initiated to increase the limited knowledge on links between environmental contaminants and reproductive and child health. Mother–child pairs came from two distinct geographical regions, but a single protocol was used to obtain child outcomes and to assess a large set of contaminant levels in maternal sera. We analyzed our data with a

Table 2 Varimax rotated factor pattern (factor loadings) of maternal serum levels of 16 environmental contaminants

	PC1 PFAS-PC1	PC2 DiNP metabolites	PC3 DEHP metabolites	PC4 Organo-chlorines	PC5 PFAS-PC5
Variance explained (%)	21.3	14.1	13.3	11.6	9.7
PFDA	**0.830**	0.031	0.021	0.277	0.167
PFUnDA	**0.809**	0.064	−0.039	0.258	−0.064
PFNA	**0.743**	−0.018	0.002	0.324	0.271
PFDoDA	**0.739**	0.122	−0.114	0.145	−0.261
PFOS	**0.697**	−0.044	0.048	0.143	**0.461**
PFHxS	**0.466**	−0.106	0.091	−0.128	0.254
MOiNP	−0.090	**0.847**	0.157	0.003	0.021
MCiOP	0.036	**0.798**	0.134	0.065	0.155
MHiNP	0.089	**0.787**	0.092	−0.102	−0.068
MEOHP	−0.003	0.205	**0.927**	0.013	0.008
MEHHP	−0.011	0.027	**0.894**	−0.041	0.024
MECPP	0.013	**0.448**	**0.620**	0.012	−0.024
p,p′-DDE	0.281	−0.040	−0.030	**0.877**	0.103
PCB 153	0.326	−0.009	0.010	**0.864**	0.057
PFOA	0.239	0.023	0.053	−0.023	**0.794**
PFHpA	−0.003	0.076	−0.048	0.141	**0.658**

Factor loadings greater than 0.4 or less than −0.4 are shown in bold type.

PCA approach to deal with correlated exposures and to reduce the number of comparisons. Nevertheless, we still tested 25 associations (5 asthma/eczema outcomes and 5 uncorrelated PC scores), which may have resulted in false-positive findings. Three associations were statistically significant at the 0.05 level in the Greenlandic or the Ukrainian cohort, with an opposite direction of association in the other cohort. For example, in children from Greenland, a negative association was found between PC4 (organochlorines) and ever eczema (OR 0.78, 0.61–0.99), whereas a positive association was found in children from Ukraine (OR 1.30, 0.87–1.94). Even though large differences exist between the two populations in terms of symptom prevalence, exposure levels, and covariate patterns, these differences do not provide a likely explanation for opposite findings. The association between DiNP metabolites and current eczema was the only statistically significant result when using meta-analysis to combine the population-specific estimates, showing consistent, albeit modest, inverse associations in both populations. Murine models have yielded conflicting results regarding the effects of postnatal exposure to phthalates on immune and inflammatory responses (3). Prenatal exposure to DEHP reduced asthmatic responses in the offspring, but prenatal exposure to DiNP has not been studied in mice (32). Thus, it is not clear whether the negative relationship between DiNP and eczema might be a causal (immunotoxic) effect, or due to chance.

We assessed prenatal exposure levels in a single serum sample, on average at the end of the second trimester. Misclassification of prenatal exposure levels is a larger concern for phthalates, which have a short half-life, than for the other compounds that are relatively stable over time. An interview-based questionnaire was conducted when the children had reached the age of 5–9 years, but postnatal contaminant levels were not measured. Although prenatal exposures may affect the developing immune system and thereby cause long-lasting effects, it could be conceived that physiological effects in early life weaken over time. In a meta-analysis, the association between maternal or cord blood DDE and wheeze was only found before 18 months (18). Grandjean et al. (33) found that negative associations between PFAS exposures and antibody responses to childhood immunizations were more pronounced for exposures measured at age 5 years than for prenatal exposures. Other studies investigated postnatal phthalate (5–10, 34, 35) and PFAS (36, 37) exposures in children and adolescents in relation to allergic outcomes. Several studies found positive associations between the presence of PVC flooring or phthalates in house dust and asthma or allergy in children (5–8). Modest positive associations of a DiNP and a diisodecyl phthalate metabolite with asthma were found in 10-year-old Norwegian children (10), while a DEHP and a dibutyl phthalate metabolite correlated with asthma and allergy in Taiwanese children (8). Other studies found inverse or no associations between phthalate metabolites in urine samples and allergic outcomes in children (34, 35). A Taiwanese case–control study in 10- to 15-year-old children found positive associations between PFASs and asthma outcomes (36), but no clear evidence of an increased risk due to PFAS exposures was found in US adolescents (37).

There are some disadvantages of using serum instead of urine to determine phthalate exposure (38). If the serum sample becomes contaminated after collection with the ubiquitous diesters of phthalate, the lipase activity of serum will split the diesters into monoesters. The concentrations of monoesters in serum are therefore not reliable measures of exposure, contrary to urine that has no lipase activity (39). Therefore, we did not investigate the monoesters MEHP and MiNP, nor any other phthalate monoester. Moreover, bisphenol A (BPA) was not included in our study, as BPA

Table 3 Associations of prenatal exposures to perfluoroalkyl substances (PFASs, PC1 and PC5), metabolites of diisononyl phthalates (DiNP, PC2) and diethylhexyl phthalates (DEHP, PC3), and organochlorines (PCB-153 and *p,p′*-DDE, PC4) with asthma and eczema symptoms in 492 children from Ukraine and 532 children from Greenland

		OR (95% CI), unadjusted			OR (95% CI), adjusted*		
Outcome	PC score	Ukraine	Greenland	Combined	Ukraine	Greenland	Combined
Ever asthma	PFAS-PC1	1.03 (0.41–2.59)	0.93 (0.72–1.20)	0.94 (0.73–1.19)	1.00 (0.39–2.59)	0.91 (0.70–1.17)	0.91 (0.71–1.17)
	DiNP metabolites	0.82 (0.42–1.60)	1.05 (0.72–1.54)	0.99 (0.71–1.38)	0.85 (0.42–1.72)	1.05 (0.71–1.54)	1.00 (0.71–1.40)
	DEHP metabolites	0.87 (0.47–1.61)	0.77 (0.55–1.08)	0.79 (0.59–1.07)	0.87 (0.48–1.60)	0.80 (0.57–1.12)	0.81 (0.61–1.09)
	Organochlorines	1.31 (0.45–3.81)	0.96 (0.76–1.21)	0.97 (0.78–1.22)	1.19 (0.40–3.58)	0.95 (0.76–1.20)	0.96 (0.77–1.20)
	PFAS-PC5	0.67 (0.35–1.27)	0.80 (0.60–1.06)	0.77 (0.60–1.01)	0.69 (0.35–1.33)	0.87 (0.64–1.17)	0.83 (0.63–1.10)
Ever eczema	PFAS-PC1	1.09 (0.79–1.50)	1.03 (0.80–1.34)	1.05 (0.86–1.29)	1.05 (0.75–1.47)	1.03 (0.77–1.36)	1.04 (0.84–1.29)
	DiNP metabolites	0.86 (0.69–1.06)	0.89 (0.60–1.32)	0.86 (0.71–1.04)	0.90 (0.72–1.13)	0.89 (0.59–1.34)	0.90 (0.74–1.09)
	DEHP metabolites	1.10 (0.89–1.37)	0.93 (0.67–1.29)	1.05 (0.87–1.26)	1.13 (0.90–1.41)	0.73 (0.50–1.06)	1.00 (0.83–1.22)
	Organochlorines	1.30 (0.88–1.90)	**0.79 (0.63–0.99)**	0.90 (0.74–1.09)	1.30 (0.87–1.94)	**0.78 (0.61–0.99)**	0.89 (0.72–1.10)
	PFAS-PC5	0.93 (0.74–1.17)	1.10 (0.82–1.47)	0.99 (0.83–1.19)	0.94 (0.74–1.19)	0.94 (0.68–1.30)	0.94 (0.77–1.14)
Ever wheeze	PFAS-PC1	0.80 (0.51–1.27)	0.92 (0.74–1.14)	0.90 (0.74–1.09)	0.73 (0.46–1.18)	0.93 (0.75–1.16)	0.89 (0.73–1.09)
	DiNP metabolites	1.00 (0.76–1.31)	1.14 (0.84–1.55)	1.06 (0.86–1.30)	1.02 (0.77–1.35)	1.17 (0.85–1.61)	1.08 (0.88–1.34)
	DEHP metabolites	1.31 (0.97–1.76)	0.97 (0.73–1.27)	1.11 (0.91–1.36)	1.28 (0.95–1.74)	1.00 (0.74–1.33)	1.12 (0.91–1.39)
	Organochlorines	0.81 (0.48–1.37)	0.85 (0.70–1.03)	0.85 (0.71–1.01)	0.71 (0.41–1.24)	0.86 (0.70–1.04)	0.84 (0.70–1.01)
	PFAS-PC5	0.89 (0.65–1.23)	0.95 (0.75–1.22)	0.93 (0.77–1.13)	0.86 (0.62–1.19)	0.94 (0.73–1.20)	0.91 (0.75–1.11)
Current wheeze	PFAS-PC1	0.90 (0.47–1.75)	0.79 (0.55–1.15)	0.82 (0.59–1.13)	0.84 (0.42–1.65)	0.73 (0.48–1.10)	0.75 (0.53–1.07)
	DiNP metabolites	0.91 (0.61–1.36)	1.02 (0.60–1.74)	0.95 (0.69–1.31)	0.93 (0.62–1.40)	1.07 (0.59–1.92)	0.98 (0.70–1.36)
	DEHP metabolites	**1.53 (1.02–2.29)**	0.75 (0.46–1.24)	1.15 (0.84–1.58)	**1.56 (1.03–2.37)**	0.71 (0.42–1.19)	1.15 (0.83–1.59)
	Organochlorines	1.11 (0.53–2.32)	1.01 (0.72–1.42)	1.03 (0.76–1.40)	1.06 (0.49–2.29)	1.12 (0.79–1.59)	1.11 (0.81–1.53)
	PFAS-PC5	**0.63 (0.41–0.98)**	1.26 (0.81–1.96)	0.89 (0.65–1.22)	**0.64 (0.41–0.99)**	1.33 (0.82–2.17)	0.89 (0.64–1.23)
Current eczema	PFAS-PC1	1.59 (0.89–2.85)	0.93 (0.71–1.23)	1.03 (0.80–1.32)	1.57 (0.87–2.86)	0.96 (0.73–1.27)	1.05 (0.82–1.35)
	DiNP metabolites	0.75 (0.49–1.14)	**0.64 (0.41–0.99)**	**0.69 (0.51–0.94)**	0.76 (0.50–1.16)	0.65 (0.42–1.01)	**0.71 (0.52–0.96)**
	DEHP metabolites	1.13 (0.77–1.64)	0.98 (0.69–1.39)	1.04 (0.81–1.35)	1.16 (0.78–1.74)	0.98 (0.69–1.39)	1.05 (0.81–1.37)
	Organochlorines	1.27 (0.64–2.52)	0.95 (0.74–1.21)	0.98 (0.78–1.23)	1.30 (0.65–2.59)	0.98 (0.76–1.25)	1.01 (0.80–1.27)
	PFAS-PC5	0.81 (0.54–1.23)	1.08 (0.79–1.47)	0.97 (0.76–1.25)	0.82 (0.54–1.24)	1.03 (0.73–1.43)	0.94 (0.73–1.22)

Data are presented as odds ratios and 95% confidence intervals for a 1 SD change in principal component (PC) score. Fixed-effects meta-analysis was used to combine the population-specific estimates. Bold type represents *P*-values < 0.05.

*Adjusted for maternal allergy, smoking during pregnancy, educational level, maternal age, child sex, child age at follow-up, gestational age at blood sampling, parity, breastfeeding, and birthweight.

levels in serum were below the LOD (0.2 ng/ml) in 54% of the samples. Secondary oxidative metabolites of phthalates can be reliably assessed in serum, as they are not susceptible to lipase activity and external contamination. Although metabolite levels in serum are much lower than in urine, most of our samples were above the LODs.

We used questionnaire data to assess eczema and asthma symptoms at one point in time, which has inherent limitations, such as recall bias and misclassification. Moreover, we could not distinguish different wheezing or asthma phenotypes. We used items from the ISAAC questionnaire, which is an instrument widely used to assess asthma and eczema in children worldwide, and interviews were mainly conducted by pediatricians and other medical professionals. The prevalence of symptoms in both populations falls within the global variation as reported in ISAAC Phase Three. As prenatal exposure levels were not known by the parents or the doctors who conducted the interviews, there is no reason to believe that any misclassification of health outcomes would be differential by exposure status. However, nondifferential misclassification of health outcomes and prenatal exposure levels may have resulted in a bias toward the null and reduced statistical power. Thus, despite the relatively large size of our birth cohort, and the standardized assessment of outcomes and

exposures, we cannot exclude the possibility of false-negative findings.

We used a PCA method to reduce the dimensionality of the exposure matrix. The PCA method maximizes the variance in the exposure matrix without considering the association with the outcome of interest. This may have resulted in less optimal exposure–disease factors (40). However, as we researched several different outcomes and wanted to derive components that would be transferable between populations, we opted for the PCA method instead of methods such as partial least-squares regression techniques.

In conclusion, we used a multipollutant approach to assess the associations between prenatal exposure levels and asthma and eczema in children from two distinct geographical regions. A meta-analysis of the two populations suggested a modest inverse association between DiNP metabolites and current eczema. Further research, preferably addressing multiple exposures that are measured both prenatally and postnatally, is needed to shed more light on the possible contribution of emerging and legacy pollutants to allergic disorders in children.

Author contributions

LAMS, VL, RV, and DH involved in the conception and design of the current analysis. BBH, HSP, IL, BAGJ, JPB, and GT designed or collected data for the cohort study. BAGJ and CHL performed chemical analyses. LAMS analyzed the data and drafted the manuscript. All authors, particularly VL, BBH, BAGJ, JPB, GT, RV, and DH participated in the interpretation of results and revision of the manuscript. All authors approved the final version of the manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary Methods and References.

Table S1. Characteristics of environmental contaminants included in the present study.

Table S2. Limit of detection (LOD) of analyzed contaminants of 492 Ukrainian and 532 Greenlandic mothers, INUENDO birth cohort.

Table S3. Number of missing values in child outcomes and covariates in 492 Ukrainian and 532 Greenlandic mother–child pairs from the INUENDO birth cohort.

Table S4. Univariate associations between prenatal exposures to environmental contaminants and asthma and eczema symptoms in 492 Ukrainian and 532 Greenlandic children.

Figure S1. Pearson correlation matrix of maternal serum levels of 16 environmental contaminants.

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