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Maternal exposure to per- and polyfluoroalkyl substances and epitope level antibody response to vaccines against measles and rubella in children from the Boston birth cohort

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ABSTRACT

Background: Previous studies suggest that per- and polyfluoroalkyl substances (PFAS) may act as immune suppressants. However, research about the impact of PFAS exposure on antibody responses to the measles, mumps, rubella (MMR) vaccine is limited and inconsistent.

Methods: This report includes 748 mother–child pairs from the Boston Birth Cohort, with 8 PFAS compounds measured in maternal plasma shortly after delivery. IgG reactivities to measles and rubella were profiled in cord blood and venous blood plasma during early childhood, using Phage ImmunoPrecipitation Sequencing. Linear regression models were applied to assess the relationships between log2-transformed PFAS and IgG reactivities as measured by Viral Aggregate Reactivity score (VARscore, with inverse normal transformation) for measles and rubella. Quantile g-computation was applied to evaluate the PFAS mixture – VARscore associations.

Results: The detection rate for 8 PFAS compounds ranged from 90 % to 100 % in maternal plasma. Maternal PFAS burden score ($P = 0.01$), but not individual PFAS compounds, was associated with lower VARscore for measles in cord blood. In 348 children after receiving the MMR vaccine, three maternal PFAS compounds (Me-PFOSA-AcOH, PFHpS and PFHxS) were significantly associated with lower measles VARscore ($P < 0.05$). Me-PFOSA-AcOH and PFHxS were significantly associated with higher risk of having low reactivity to measles defined as VARscore < 25th percentile. PFAS mixture analysis revealed a significant inverse association between quantile of the PFAS mixture and measles VARscore ($P = 0.025$) in children after vaccination, with PFHxS as an important contributor to this association. These inverse associations were more pronounced in Black children (compared to non-Black children) and in preterm children (compared to term children). In comparison, no associations were found for rubella VARscore.

Conclusions: This prospective birth cohort study provides suggestive evidence that maternal PFAS exposure is associated with a reduced immune response to the measles vaccine, especially, among Black or preterm children.

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large class of thousands of synthetic chemicals widely used in various industries due to their water- and grease-resistant properties (EPA, 2018, 2024). Their persistence in the environment is a significant concern, because they do not break down easily and can remain in the environment for decades, leading to widespread contamination in drinking water, soil, living organisms, commercial household products, and foods (Buck et al. 2011). Multiple PFAS are nearly universally detected in the blood of individuals in the US (Kato et al. 2015). Notably, these substances can be transferred from mothers to fetuses via the placenta (Gutzkow et al., 2012; Manzano-Salgado et al., 2015) and to infants through breastfeeding (Mogensen et al. 2015b; Papadopoulou et al. 2016; Thomsen et al. 2010), raising concern about early-life exposure and its potential health impacts later in life.

Routine childhood vaccinations are critical for preventing infectious diseases like measles, mumps, rubella, tetanus, and diphtheria. Increasing evidence indicates that PFAS have immune-suppressive effects (DeWitt et al. 2019) and may reduce the body's ability to mount an adequate immune response to these vaccines (Crawford et al. 2023; Zhang et al. 2022). A few epidemiologic studies have investigated the relationships between PFAS exposure prenatally (Granum et al. 2013; Sigvaldsen et al. 2024; Zell-Baran et al. 2023) or during childhood (Grandjean et al. 2012; Grandjean et al. 2017a; Mogensen et al. 2015a; Sigvaldsen et al. 2024; Timmermann et al. 2022) and antibody response to different vaccines, with the major focus on tetanus (Abraham et al. 2020; Crawford et al. 2023; Grandjean et al. 2012; Grandjean et al. 2017a; Grandjean et al. 2017b; Mogensen et al. 2015a; Sigvaldsen et al. 2024; Timmermann et al. 2022) and diphtheria vaccines(Abraham et al. 2020; Crawford et al. 2023; Grandjean et al. 2012; Grandjean et al. 2017a; Grandjean et al. 2017b; Mogensen et al. 2015a; Sigvaldsen et al. 2024; Timmermann et al. 2022). However, such studies on the measles, mumps and rubella (MMR) vaccine are limited, and the findings are inconclusive (Granum et al. 2013; Sigvaldsen et al. 2024; Zell-Baran et al. 2023). For example, a study in 50 Norwegian children receiving one dose of the MMR vaccine reported that prenatal perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexanesulfonic acid (PFHxS) were inversely associated with the child's rubella antibody level, but not with measles antibody level (Granum et al. 2013). Similar associations for rubella were reported by Stein et al in 1,191 US adolescents using a cross-sectional study design (Stein et al. 2016), but not by others. PFOS and perfluorodecanoic acid (PFDeA) exposure in infancy were reported to have significant associations with measles IgG titers in Guinea – Bissau children following a single dose of the vaccine (Timmermann et al. 2020), and maternal PFNA was inversely associated with measles IgG titers after two doses of vaccines in the Healthy Start Cohort study in Colorado (Zell-Baran et al. 2023). In comparison, three other studies (Granum et al. 2013; Sigvaldsen et al. 2024; Stein et al. 2016) observed no associations between four PFAS (PFOA, PFNA, PFHxS and PFOS) and measles IgG titers. The inconsistent findings across different studies may be partly attributed to several limitations, such as small sample sizes, different population characteristics, a limited number of PFAS compounds analyzed in some studies and insufficient control of confounding variables. Furthermore, the influence of potential effect modifiers has often been overlooked.

In a US urban, low-income, racially diverse prospective Boston Birth Cohort (BBC), we utilized VirScan (Mina et al. 2019; Xu et al. 2015), an advanced Phage ImmunoPrecipitation Sequencing (PhIP-Seq) technology, to quantify IgG antibody reactivity to viruses including measles, mumps and rubella in cord plasma as well as in venous plasma during early childhood aged 6 months to 5 years of old. This technology has been successfully applied to investigate the impact of measles virus infection on antibody repertoire(Mina et al. 2019). The goals of this study were to investigate the relationships of maternal PFAS levels shortly after delivery with 1) maternal-transferred IgG reactivity for measles, mumps and rubella in cord blood; 2) IgG reactivity for each virus during early childhood in children before vaccination; and 3) IgG reactivity for each virus during early childhood in children after vaccination. The PFAS compounds were analyzed individually and as a mixture. Additionally, we explored whether the identified associations were modified by factors such as maternal race and ethnicity, preterm birth (PTB), sex, and feeding modality during infancy.

2. Methods

2.1. Study population

The parent study cohort, the BBC (registered in ClinicalTrial.gov NCT03228875) was initiated in 1998 with rolling enrollment at the Boston Medical Center (BMC) in Boston, MA. Details about this cohort, enrollment procedures and study design have been reported elsewhere (Hong et al. 2025; Pearson et al. 2022). Briefly, women who delivered a singleton live infant at BMC 24–72 h postpartum were recruited into this cohort. After providing written informed consent, data on maternal sociodemographic characteristics, lifestyle, and medical history were obtained by research assistants based on standardized questionnaires, and maternal venous blood samples and cord blood samples were obtained. Maternal and newborn clinical information, including birth outcomes, was abstracted from electronic medical records (EMRs). The BBC mirrors the patient population of the BMC and is enriched by PTBs. Postnatal follow-up in the BBC has been ongoing since 2004. The study team worked with data warehouse specialists semi-annually to abstract EMRs of study children. The study protocol received approval from the Institutional Review Boards of BMC and the Johns Hopkins Bloomberg School of Public Health.

Participant enrollment of the current study is presented in Fig. 1. Out of 3,416 mother–child pairs in the BBC, 2 were excluded due to missing questionnaire interview, and then, 1,333 mothers were selected for maternal PFAS measurement. A total of 982 children with available plasma samples during early childhood (0.5–5 years) were processed for IgG antibody profiling at birth and during early childhood, leading to 823 children having both maternal PFAS data and IgG antibody data during early childhood. We then removed 75 children from subsequent analyses, including 11 who received the MMR vaccine within the first 6 months of age ($n = 1$) or within 2 weeks before IgG profiling ($n = 10$), 51 who had unclear MMR vaccine records and 13 children without available IgG antibody profiles in cord plasma. The remaining 748 children were further classified into two groups: 1) 400 "pre-vaccination" children who had not yet received the MMR vaccine at the time of IgG profiling; 2) 348 "post-vaccination" children, including 319 children with clear MMR vaccination records abstracted from EMRs (303 with the first dose and 16 with both doses of MMR vaccines administered > 2 weeks prior to IgG antibody profiling), and 29 children who likely received the vaccine. The latter 29 children, although with missing EMRs, met all the following criteria: aged > 15 months at the time of IgG profiling, IgG reactivity for measles, mumps, or rubella in childhood higher than in cord blood in the same child and higher than the median value observed in 325 children with clear MMR vaccine records. Population characteristics of the 748 children included in this study was largely comparable with those of the BBC children not included in this study, except for a higher gestational age and a lower percentage of PTBs in the included group (**Table S1**).

2.2. PFAS measurement

PFAS concentration was measured in maternal postpartum plasma from 1,333 mothers meeting the following criteria 1) having available plasma samples; 2) the index child has been enrolled and followed since birth; 3) the index child had archived plasma collected both at birth and during early childhood for multi-omic studies. The population

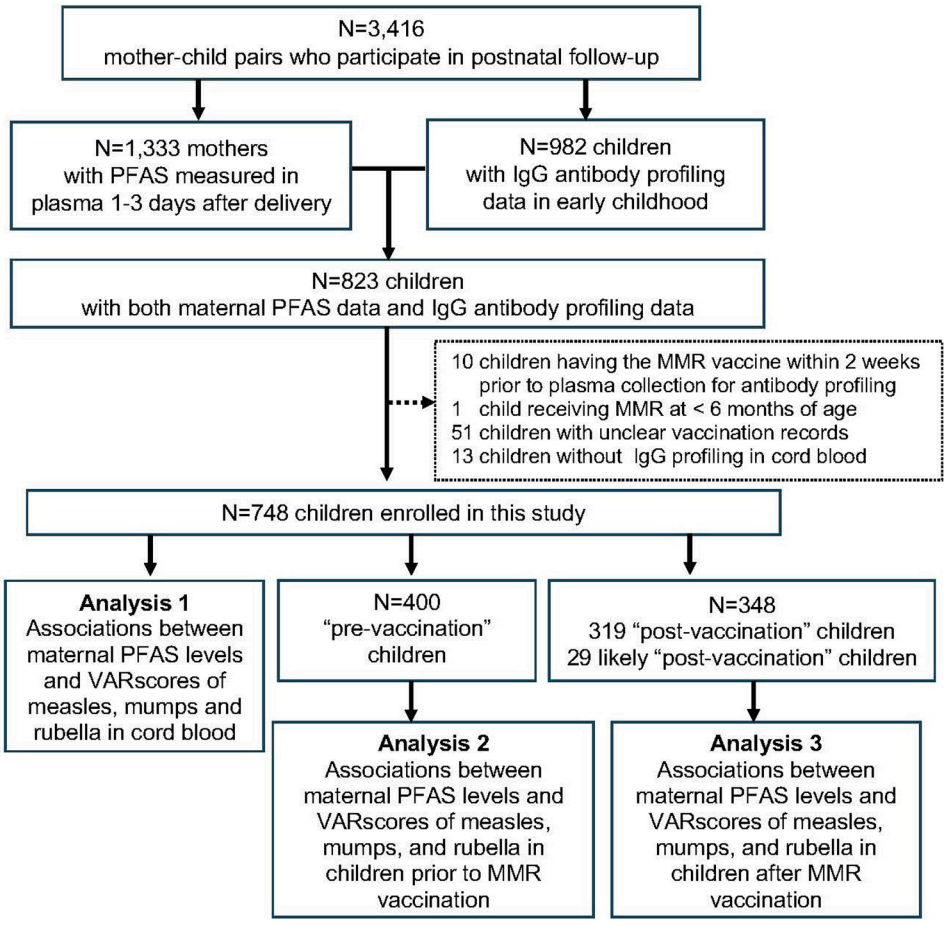

Fig. 1. Flow chart of participant enrollment in this study.

characteristics of the 1,333 mothers selected for PFAS measurement were largely comparable with those of all the mothers enrolled in the BBC, except that the proportion of preterm birth was relatively lower. The laboratory procedure has been reported recently (Li et al. 2024). Briefly, 12 PFAS compounds (**Table S2**) were measured using an online solid-phase extraction unit (PICO, Spark Holland, Amsterdam, Netherlands) coupled to a high- or ultra high-performance liquid chromatography-tandem mass spectrometry at New Jersey Department of Health-Public Health and Environmental Laboratories-Environmental and Chemical Laboratory Services, following the same lab procedure and Quality Assurance and Quality Control steps as reported previously (Li et al. 2024; Yu et al. 2017; Yu et al. 2021). Coefficients of variation (CVs) were below 20 % and relative percent differences (RPD) were below 30 % in lab-spiked samples for all PFASs. PFAS had levels of detection (LOD) of 0.005–0.061 ng/mL. Eight PFAS compounds were detected in > 85 % of all maternal samples, which were the focus of this study, including 2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH), PFDeA, perfluoroheptanesulfonic acid (PFHpS), PFHxS, PFNA, PFOA, PFOS, and perfluoroundecanoic acid (PFUnA). For each compound, values below LOD were replaced with LOD/$\sqrt{2}$ for next-step analyses. To quantify total exposure burden, PFAS burden score (deciles with summed isomers) was then calculated from 7 PFAS (Me-PFOSA-AcOH, PFUnA, PFDeA, PFHxS, PFNA, PFOA and PFOS) based on nationally representative U.S. reference ranges from 2017 to 2018, using the formula as reported previously (Liu et al. 2022).

2.3. Anti-viral IgG antibody profiling

Cord blood and venous blood samples were collected, and plasma were separated and stored at −80 °C until IgG profiling using PhIP-Seq which has been previously described in detail (Morgenlander et al. 2024; Xu et al. 2015). Briefly, a T7 bacteriophage display library was constructed to cover the human virome, which consists of 106,678 56-aa peptide tiles. Each peptide was encoded by a member of a DNA oligonucleotide library that was synthesized (Twist Bioscience) and cloned into the T7 bacteriophage display system. Next, 0.2ul of sample plasma was incubated with the T7 phage library, allowing antibodies to bind their target peptides displayed on the phage. All desired antibodies (IgG in this study) and bound phages were captured with magnetic beads coated by protein A and protein G. Peptide coding DNA from antibody bound phages was amplified and sequenced on an Illumina NovaSeq 6000.

In the VirScan library, there are 410, 234 and 439 peptides for measles, mumps and rubella, respectively. To facilitate the interpretation of complex antibody profiles measured with VirScan, an aggregate reactivity algorithm was developed to provide a virus-level metric of antibody reactivity. As reported previously, this algorithm integrates the intensity and breadth of antibody response to all peptides for each virus to generate a Viral Aggregate Reactivity score (VARscore), which is calculated by comparing the average fold changes of peptides covering each virus to distributions of average fold change from randomly selected peptides (Morgenlander et al. 2024). The algorithm adjusts for host, batch and library factors which may otherwise confound comparison of PhIP-Seq results, and is a metric to quantify the overall strength of an antibody response to a virus. The VARscore algorithm was applied to the VirScan data of 615 samples from healthy individuals (Venkataraman et al. 2022), and can effectively distinguish viruses that are expected to be frequently targeted by antibodies from those that are expected to be less commonly targeted by antibodies in this population (Morgenlander et al. 2024).

2.4. Covariates

Maternal sociodemographic variables including maternal race and ethnicity, education, smoking status, and diet information were collected via questionnaire interview at enrollment. Maternal Mediterranean-Style Diet score (MSDS) was calculated as reported(Rhee et al. 2021). Delivery mode, child's sex and gestational age at delivery were abstracted from EMRs. At each visit during early childhood, maternal questionnaire interview was applied to collect feeding modality ("exclusively formula-fed", "exclusively breast-fed" for at least the first four months, and "both formula-fed and breast-fed"), which was further classified as "exclusively formula-fed" vs "any breastfed" by combining "both formula-fed and breast-fed" and "exclusively breast-fed" into the "any breastfed" group. There were a few categorical variables having a small proportion of missing data (< 5 %, **table S1**), which were imputed as the most frequent category for subsequent analyses.

Confounding variables were selected based on both a priori knowledge (maternal race and ethnicity, sex and PTB) and through a directed acyclic graph (DAG). As shown in **Fig. S1**, a DAG was constructed to illustrate relationships between maternal PFAS exposure and IgG antibody response to MMR vaccination (outcomes) in various stages: in cord blood, in pre-vaccination childhood, and in post-vaccination childhood, respectively. Bivariate analyses were performed to explore the associations of each potential confounder (including maternal education, maternal age at delivery, pre-pregnancy BMI, maternal smoking during pregnancy, MSDS, maternal folate level measured within 1–3 days after delivery, parity, delivery mode, feeding modality, child age at blood collection for IgG profiling, and time since vaccination to blood collection for IgG profiling) with PFAS exposure and each outcome (VARscore), and those which were associated with both PFAS exposure and an outcome at $P < 0.1$ were selected for covariate adjustment in subsequent analyses. Three different sets of covariates were adjusted in the final model, including one set for analyses of VARscore in cord blood (maternal race and ethnicity, sex, PTB, maternal age at delivery, and MSDS), one set for analyses of childhood VARscore in pre-vaccination children (maternal race and ethnicity, sex, PTB, and child's age at blood collection for IgG profiling) and one set for analyses of childhood VARscore in post-vaccination children (maternal race and ethnicity, sex, PTB, maternal age at delivery, delivery mode, maternal smoking during pregnancy, feeding modality, and times since last vaccination to blood collection for IgG profiling). Delivery mode was adjusted in the model which was reported to have impact on vaccine response(Wang et al. 2024). For those 29 children with likely vaccination, times since vaccination was imputed as child's age at the time of IgG profiling minus median of child's age at the time of vaccination which was calculated based on the 325 children with clear MMR vaccine records.

2.5. Statistical analyses

Population characteristics were presented in "pre-vaccination" children and "post-vaccination children", separately. Pair-wise correlations among the 8 maternal PFAS compounds were estimated using Spearman's rank correlation. Distribution of each PFAS was skewed and were therefore log2-transformed to reduce the impact of outliers on subsequent analyses. When VARscore for each virus was analyzed as a continuous outcome, the rank-based inverse normal transformation was applied to approximate normal distribution. Linear regression models were applied to investigate the associations of each individual maternal log2-transformed PFAS compound or PFAS burden score with inversely normalized VARscores for each virus in cord plasma from 748 children, in venous plasma from 400 pre-vaccination children, and in venous plasma from 348 post-vaccination children, respectively, adjusting for covariates as mentioned above. Stratified analysis and interaction tests were further performed to explore potential modifiers, including maternal race and ethnicity, prematurity, sex and feeding modality ("exclusively formula-fed" vs "any breastfed"). The above analyses were further repeated using the logistic regression model, with low IgG reactivity to measles and rubella (defined as VARscore < 25th percentile) as the binary outcomes.

We then applied quantile g-computation to evaluate the overall effects of maternal PFAS mixture on each inversely normalized VARscore, using the R package "qgcomp" (Keil et al. 2020). All PFAS mixture components were log2-transformed, centered and scaled, and a linear regression model was fit for quartiles of the mixture of PFAS, adjusting for the same covariates as mentioned above. The overall effect of maternal PFA mixture on the risk of having low IgG reactivity to each virus was also analyzed by fitting a logistic regression model. Weight (either positive or negative) for each PFAS component generated by the model were shown to represent the relative magnitude and direction of associations between each PFAS component and the outcomes. These analyses were performed using R version 4.5.0.

3. Results

Among the 748 children, 55.7 % were born to non-Hispanic Black mothers, 17.1 % were born preterm, 48.3 % were male, and 23.6 % were exclusively formula-fed (**Table S1**). The median age (interquartile range) at the time of IgG profiling during childhood was 1.1 (0.8 – 2.2) years. Population characteristics for 400 pre-vaccination children and 348 post-vaccination children were shown in Table 1. While the two groups were comparable in terms of most population characteristics, post-vaccination children were more likely to be born to nulliparous

Table 1
Maternal and child characteristics in 748 children enrolled in this study, stratified by vaccination status.

Population characteristics [a]	Pre-vaccination children	Post-vaccination children	P [a,b]
N	400	348	
Maternal age at delivery (years), M ± SD	28.4 ± 6.0	28.2 ± 6.6	0.550
Maternal race: non-Hispanic Black, n (%)	217 (54.2)	200 (57.5)	0.417
Maternal marriage status, married, n (%) [c]	129 (32.2)	115 (33.0)	0.878
Maternal education, < high school, n (%) [c]	100 (25.0)	102 (29.2)	0.214
Pre-pregnancy BMI category, n (%) [c]			0.468
Normal weight	200 (50.0)	182 (52.3)	
Overweight	107 (26.8)	98 (28.2)	
Obese	93 (23.2)	68 (19.5)	
Parity, nulliparous, n (%)	141 (35.2)	164 (47.1)	0.001
Maternal ever smoking during pregnancy, n (%) [c]	76 (19.0)	53 (15.2)	0.206
Maternal Mediterranean-Style Diet score, M ± SD	24.5 ± 4.0	25.0 ± 4.0	0.117
Gestational age (weeks), Median (IQR)	39.0 (37.6–39.9)	39.2 (37.6–40.3)	0.097[b]
Preterm birth (< 37 weeks), n (%)	68 (17.0)	60 (16.9)	1.000
Mode of delivery, cesarean section, n (%)	145 (35.6)	127 (35.9)	1.000
Child's sex, male, n (%)	193 (48.2)	168 (48.3)	1.000
Feeding modality: exclusively formula-fed, n (%)[c]	103 (25.8)	72 (20.7)	0.123
Child's age at IgG profiling (years), Median (IQR)	0.82 (0.76–0.95)	2.3 (1.68–3.20)	<0.001[b]

IQR: Inter-quartile range.

[a,b] The differences in population characteristics between pre-vaccination and post-vaccination children were compared using the *t*-test for continuous variables (or [b] the Kruskal-Wallis Rank Sum test for continuous variables with non-normal distribution), and the chi square test for categorical variables, respectively.

[c] These categorical variables have missing data in < 5 % samples (see Table S1) and were imputed as the most-frequent category.

mothers (47.1 % vs 35.2 %) and were older at the time of IgG profiling (All $P < 0.05$) than pre-vaccination children.

Three PFAS compounds (PFHxS, PFNA and PFOS) were detected in all mothers; and the remaining five were detected in > 90 % of the enrolled mothers, with distribution shown in **Fig. S2.** Median maternal PFAS concentrations ranged from 0.12 for Me-PFOSA-AcOH to 4.0 ng/mL for PFOS, which were generally comparable with data from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) as we reported recently.(Li et al. 2024) Correlation coefficients for each pair of PFAS compounds ranged from −0.01 to 0.85, with most exhibiting moderate correlations (**Fig. S2**). PFAS burden score was highly correlated with PFDeA and PFNA (r > 0.80) but had modest-to-moderate correlation with Me-PFOSA-AcOH and PFHxS (r < 0.40, **Fig. S2**).

Fig. 2 illustrates the distribution of measles, mumps and rubella VARscores in children at various time periods. At birth, each VARscore in cord plasma showed a broad range of variation, indicating that the passive immunity at birth is quite variable. In 400 pre-vaccination children, the VARscores during early childhood were generally lower than those observed at birth, suggesting a decrease in passive immunity. As expected, post-vaccination children (n = 348) had significantly higher VARscores for measles and rubella than pre-vaccination children, which may reflect the immune response stimulated by MMR vaccination; In comparison, the VARscore for mumps in post-vaccination children was low and had no significant difference when compared to pre-vaccination children, which may indicate that there were no reliable post-vaccine VARscore signals. Analyses of mumps VARscore were removed from subsequent analyses.

3.1. Maternal PFAS associations with inversely normalized VARscores in cord blood, and in childhood before vaccination

Among 748 children, we observed that maternal PFDeA and PFAS burden score tended to be inversely associated with measles VARscore in cord blood, while only the inverse association for PFAS burden score was statistically significant ($P = 0.011$, **Fig. S3**). No significant associations were observed for rubella VARscores in cord blood. Additionally, in 400 "pre-vaccination" children, no significant associations were found between each maternal PFAS (including the PFAS burden score) and each VARscore (**Fig. S4**). These associations remained comparable when further adjusting for other factors such as mode of delivery, parity and maternal smoking.

3.2. Maternal PFAS associations with childhood VARscores after MMR vaccination

Among the 348 "post-vaccination" children, we found that a doubling in maternal Me-PFOSA-AcOH ($P = 0.033$), PFHpS ($P = 0.044$) and PFHxS ($P = 0.013$) each was significantly associated with lower inversely normalized measles VARscore during childhood. No significant associations were noted for rubella VARscore (Fig. 3). The results remained largely unchanged when further adjustment of the vaccine dose (**Table S3**) or when excluding the 29 children who likely received MMR vaccination (**Table S4**) or when further accounting for maternal lipid levels measured within 1–3 days after delivery (**Table S5**). When risk of having low IgG reactivity to measles (defined as VARscore < 25th percentile) was analyzed as the binary outcome, we found that a doubling in maternal Me-PFOSA-AcOH and PFHxS was associated with 1.33 (95 %CI = 1.10 – 1.61, $P = 0.003$) and 1.29 (95 %CI = 1.05 – 1.59, $P = 0.017$) higher risk of having low IgG reactivity to measles, respectively (Fig. 4).

Subgroup analyses were then conducted focusing on inversely normalized measles VARscore in 348 post-vaccination children. When stratified by maternal race and ethnicity, the inverse associations between maternal PFAS (including Me-PFOSA-AcOH, PFHpS, PFHxS and PFOA) and measles VARscore were more pronounced in Black children compared to non-Black children. Significant PFAS × race interaction effects were detected for PFHpS (P for interaction = 0.009) (Table 2). When stratified by prematurity, significant inverse associations between maternal PFAS (PFDeA, PFHpS and PFOS) and measles VARscore were observed only in preterm children, with significant PFOS × PTB or borderline significant PFDeA × PTB interaction effects (Table 3). In comparison, maternal PFHxS showed an inverse association with measles VARscore in both term and preterm children, although the association in preterm children was not statistically significant (Table 3). When stratified by feeding modality classified as "exclusively formula-fed" vs "any breastfed", we observed that PFOS was inversely associated with measles VARscore in exclusively formula-fed children but not in any breastfed children, with significant PFOS × feeding interactions (Table 4). In comparison, no significant PFAS × sex interactions were noted (**Table S6**).

3.3. Associations between the PFAS mixture and measle VARscore after MMR vaccination

In 348 post-vaccination children, every one-quartile increase in the maternal PFAS mixture was associated with a decrease of 0.18 (SD: 0.08;

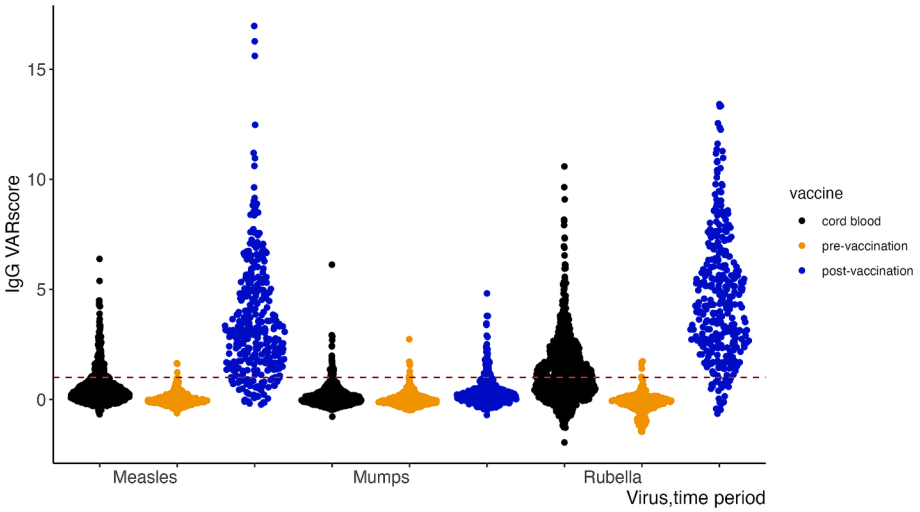

Fig. 2. Violin plots for the distribution of VARscore at birth, during early childhood from pre-vaccination children, and during early childhood from post-vaccination children, respectively. The dotted horizontal line represents VARscore of 1.

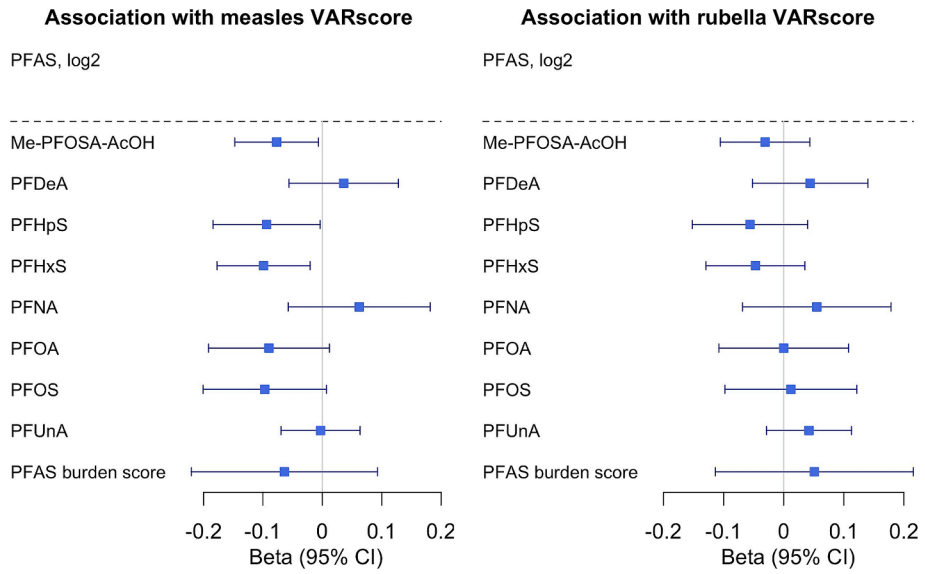

Fig. 3. Forest plots for the associations between maternal PFAS levels after delivery and inversely normalized VARscores for measles and rubella during early childhood in 348 post-vaccination children, adjusted for race and ethnicity, maternal age at delivery, maternal smoking during pregnancy, delivery type, preterm birth, feeding modality, infant's sex and years since last vaccination.

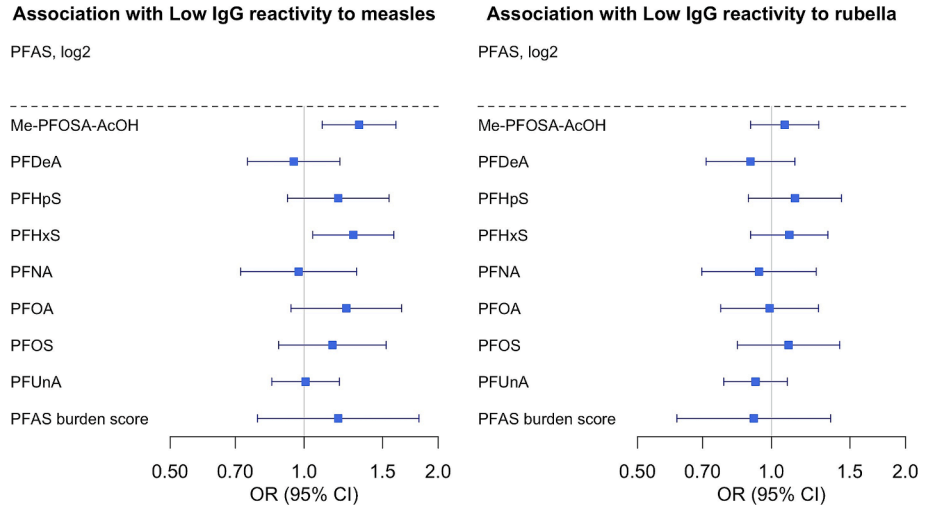

Fig. 4. Forest plots for the associations between maternal PFAS levels after delivery and risk of having low IgG reactivity to measles and rubella during early childhood in 348 post-vaccination children, adjusting for race and ethnicity, maternal age at delivery, maternal smoking during pregnancy, delivery type, preterm birth, feeding modality, infant's sex and years since last vaccination. Low IgG reactivity is defined as VARscore < 25th percentile.

$P = 0.025$) in inversely normalized measles VARscore, and PFHxS contributed the most weight to the inverse association (Fig. 5). In comparison, every one-quartile increase in the maternal PFAS mixture was associated with 1.95 higher risk of having low IgG reactivity to measles (P = 0.0036), with Me-PFOSA-AcOH contributing the most weight to this association, followed by PFHxS (Fig. 5). Additionally, the inverse association tended to be stronger in Black children than non-Black children, and in preterm children than in term children (**Fig. S5**).

4. Discussion

This inner-city prospective BBC study highlights that maternal PFAS exposure is inversely associated with the immune response to measles vaccination in children. We observed that higher maternal PFAS compound individually or as the mixture (reflecting in-utero exposure) was significantly associated with lower IgG reactivity to measles following vaccination. The observed inverse associations were more pronounced in Black children (compared to non-Black children) and in preterm children (compared to full-term children), suggesting that these factors may contribute to heightened vulnerability to immune disruption due to in-utero PFAS exposure, potentially leading to poorer vaccine responses. In comparison, maternal PFAS exposure had no or modest associations with IgG reactivity to rubella following MMR vaccination in this study.

Five studies have been conducted to examine PFAS exposure on antibody response to MMR vaccination(Granum et al. 2013; Sigvaldsen et al. 2024; Stein et al. 2016; Timmermann et al. 2020; Zell-Baran et al. 2023), three of which measured PFAS in maternal blood (Granum et al. 2013; Sigvaldsen et al. 2024; Zell-Baran et al. 2023). Granum et al found that four maternal PFAS (PFOA, PFOS, PFNA, and PFHxS) were inversely associated with rubella IgG titers but not with measles IgG in 56 Norwegian 3-year old children(Granum et al. 2013). PFAS levels were lower in the study by Granum et al than in the BBC mothers except PFOS. In 145 children aged 5 years from the Healthy Start cohort study after two doses of vaccination, Zell-Baran et al measured five maternal

Table 2
Associations between maternal plasma PFAS levels after delivery and inversely normalized measles VARscore during early childhood in 348 post-vaccination children, stratified by maternal race and ethnicity.

PFAS (log2-transformed)	Black (N = 200) Beta ± SE	*P*	Non-black (N = 148) Beta ± SE	*P*	P for interaction PFAS × race
Me-PFOSA-AcOH	−0.12 ± 0.05	0.024	−0.03 ± 0.05	0.600	0.261
PFDeA	0.03 ± 0.07	0.678	0.05 ± 0.07	0.486	0.822
PFHpS	−0.20 ± 0.06	0.002	0.07 ± 0.07	0.373	0.009
PFHxS	−0.15 ± 0.05	0.005	−0.02 ± 0.07	0.808	0.111
PFNA	0.05 ± 0.09	0.566	0.08 ± 0.09	0.350	0.767
PFOA	−0.15 ± 0.07	0.027	0.01 ± 0.08	0.879	0.138
PFOS	−0.13 ± 0.07	0.062	−0.04 ± 0.08	0.664	0.478
PFUnA	0.01 ± 0.05	0.840	−0.02 ± 0.05	0.678	0.668
PFAS burden score	−0.15 ± 0.11	0.179	0.05 ± 0.12	0.667	0.229

Adjusted for maternal age at delivery, maternal smoking during pregnancy, delivery type, preterm birth, feeding modality, infant's sex and years since last vaccination.

Table 3
Associations between maternal plasma PFAS levels after delivery and inversely normalized measles VARscore during early childhood in 348 post-vaccination children, stratified by preterm status.

PFAS Log2 transformed	Term Birth (N = 288) Beta ± SE	*P*	Preterm Birth (N = 60) Beta ± SE	*P*	P for interaction PFAS × Preterm
Me-PFOSA-AcOH	−0.07 ± 0.04	0.095	−0.13 ± 0.09	0.136	0.316
PFDeA	0.08 ± 0.05	0.114	−0.24 ± 0.12	0.042	0.054
PFHpS	−0.07 ± 0.05	0.231	−0.21 ± 0.09	0.028	0.189
PFHxS	−0.09 ± 0.04	0.032	−0.15 ± 0.11	0.175	0.637
PFNA	0.08 ± 0.07	0.233	−0.08 ± 0.16	0.620	0.703
PFOA	−0.09 ± 0.06	0.163	−0.09 ± 0.10	0.374	0.829
PFOS	−0.05 ± 0.06	0.390	−0.34 ± 0.13	0.010	0.033
PFUnA	0.02 ± 0.04	0.684	−0.13 ± 0.08	0.146	0.256
PFAS burden score	−0.02 ± 0.09	0.811	−0.33 ± 0.20	0.097	0.243

Adjusted for maternal race and ethnicity, maternal age at delivery, maternal smoking during pregnancy, delivery type, sex, breastfeeding pattern and years since last vaccination.

PFAS (PFOA, PFOS, PFNA, PFDA and PFHxS) and reported inverse associations between maternal PFNA and measles IgG titers, and between maternal PFOA and mumps IgG titers, while no associations were observed for rubella IgG(Zell-Baran et al. 2023). Both PFOA and PFNA in the study by Zell-Baran et al were about 30–50 % lower than in our study. Sigvaldsen et al reported that maternal PFAS (PFOS, PFOA, PFDA, PFHxS, PFNA) at about 8–16 weeks of gestation, all of which were higher than in the BBC mothers except for PFHxS, had no significant associations with IgG titers for measles, mumps and rubella in 841 Odense children (Sigvaldsen et al. 2024). In comparison, in 348 post-vaccination children from the BBC, we analyzed 8 maternal PFAS compounds (compared to 4–6 compounds in previous studies) and identified significant inverse associations between three PFAS compounds (Me-PFOA-AcOH, PFHpS and PFHxS) and inversely normalized measles VARscore; while no associations were found for rubella.

Earlier studies on the relationship between PFAS exposure and immune responses to MMR vaccination often had limitations due to small sample sizes and inadequate adjustment for covariates. For example, some studies (Granum et al. 2013; Sigvaldsen et al. 2024; Stein et al. 2016) did not account for time since vaccination, a potential confounder because antibody levels typically wane over time following vaccination (Kontio et al. 2012). Moreover, maternal exposure to PFAS has been linked to an increased risk of PTB(Qin et al. 2023), which, in turn, may be associated with a reduced transfer of maternal antibodies to the infant(Okoko et al. 2001). Preterm children may also have immature immune systems leading to an increased risk of infection(Melville and Moss 2013). Thus, PTB could either confound or modify the relationship between PFAS exposure and antibody responses, which waits for further investigation. Another important factor to consider is feeding modality, as breastfeeding can transfer both PFAS and antibodies from mothers to their infants, and PFAS during infancy may be higher in breastfed children than formula-fed children(Abraham et al. 2020). Furthermore, breastfeeding plays a role in the development of infant's immune system (Ames et al. 2024). Thus, in this study, we not only adjusted for PTB and feeding modality in analyses, but also explored them as potential effect modifiers. Our data suggest that the associations of maternal PFAS exposure with IgG responses to the measle vaccine vary by maternal race, prematurity and feeding modality, which may contribute to disparities in how PFAS exposure affects immune function and may partly explain the inconsistent findings observed in previous studies. Specifically, our data indicated that Black or preterm children may be more vulnerable to the immune-modulating effects of PFAS on measles immunity, which await further validation in a larger population. In addition, maternal PFOS was significantly and inversely associated with IgG response to measles in formula-fed children but not in breast-fed children, with a significant PFOS × feeding interaction.

A novel contribution of this study is the analysis of the PFAS mixture, as children are typically exposed to multiple PFAS compounds from common sources. A previous study has investigated the impact of the PFAS mixture on immune response to the MMR vaccine using quantile-based g-computation, which, however, revealed no significant associations(Zell-Baran et al. 2023). By applying the same statistical method, we found that one-quartile increase in the PFAS mixture was

Table 4
Associations between maternal plasma PFAS levels after delivery and inversely normalized measles VARscore during early childhood in 348 post-vaccination children, stratified by infant feeding modality.

PFAS (log2-transformed)	Exclusively Formula-fed (N = 72) Beta ± SE	*P*	**Any breastfed[a] (N = 272)** Beta ± SE	*P*	P for interaction PFAS × Feeding
Me-PFOSA-AcOH	−0.08 ± 0.09	0.392	−0.08 ± 0.04	0.055	0.885
PFDeA	−0.06 ± 0.15	0.702	0.04 ± 0.05	0.433	0.390
PFHpS	−0.19 ± 0.11	0.097	−0.07 ± 0.05	0.198	0.229
PFHxS	−0.18 ± 0.09	0.053	−0.07 ± 0.04	0.128	0.107
PFNA	−0.10 ± 0.19	0.590	0.08 ± 0.06	0.211	0.174
PFOA	−0.19 ± 0.12	0.097	−0.06 ± 0.06	0.418	0.184
PFOS	−0.33 ± 0.14	0.017	−0.04 ± 0.06	0.450	0.041
PFUnA	0.07 ± 0.11	0.562	−0.03 ± 0.04	0.483	0.411
PFAS burden score	−0.35 ± 0.21	0.104	−0.01 ± 0.09	0.936	0.053

Adjusted for maternal race and ethnicity, maternal age at delivery, maternal smoking during pregnancy, delivery type, sex, preterm birth and years since last vaccination

[a] This group included "both formula-fed and breast-fed" and "exclusively breast-fed" children. Four children with missing data on feeding modality were excluded from this analysis.

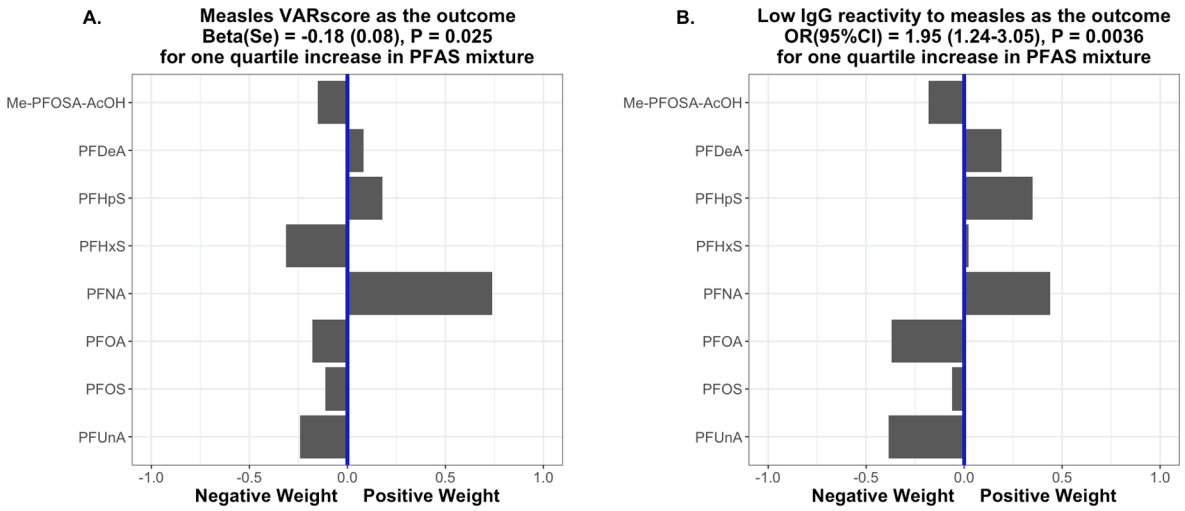

Fig. 5. Quantile-based g-computation mixture effect sizes and positive or negative weights for each maternal PFAS compound in association with inversely normalized measles VARscore or with risk of having low IgG reactivity to measles during early childhood in 348 post-vaccination children.

significantly associated with lower IgG reactivity for measles. Notably, the inverse association is mainly driven by PFHxS when inversely normalized measles VARscore was analyzed as a continuous variable. PFHxS is among the most widely used short-chain PFAS, and has been applied as a replacement for PFOA and PFOS. Although previous studies did not identify a significant association between PFHxS and measles IgG, it was associated with lower IgG levels for the rubella vaccine (Granum et al. 2013; Stein et al. 2016). In comparison, when low IgG reactivity to measles was analyzed as a binary outcome, Me-PFOSA-AcOH contributed the most weight to the identified association, followed by PFHxS. Few studies have investigated the impact of Me-PFOSA-AcOH on immune response to MMR vaccination.

We explored the impact of maternal PFAS exposure on VARscores for the two viruses in cord blood and in early childhood before vaccination. IgG antibody in cord blood is mainly transferred from the mothers via the placenta. We observed that maternal PFAS burden score was significantly and inversely associated with measles VARscore in cord blood, indicating an inverse relationship between PFAS and IgG response to measles in mothers. Since there were no epidemics of measles or rubella in the study area during the study period, IgG antibodies in the infants' system prior to vaccination may be the results of maternal-transferred antibodies and waning of the antibodies over time. The study did not find significant associations between maternal PFAS exposure and VARscores for both viruses during infancy before vaccination, which may suggest that PFAS exposure has minimal impact on the passive immunity provided to infants against measles and rubella. Another possibility is that this study may have limited statistical power to perform such analyses in pre-vaccination children since the pre-vaccination children had low VARscore to both measles and rubella, indicating that most of them were sero-negative to these viruses.

The biological mechanisms by which maternal PFAS exposure may influence a child's immune response to vaccination remain incompletely understood, but some potential pathways have been proposed (Ehrlich et al. 2023). In animal models, PFAS such as PFOA and PFOS have been reported to alter innate and adaptive immune responses including effects on inflammation, cytokine production (DeWitt et al. 2012), and changes in the expression of key immune regulatory proteins such as peroxisome proliferator-activated receptor alpha(Corsini et al. 2012; Zhu et al. 2015). Exposure to PFAS may alter the activation of critical signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells(Corsini et al. 2012), which is essential for immune cell activation and function. Evidence also suggests that PFAS can suppress the production of IgM and IgG, and alter the glycosylation patterns of IgG (Liu et al. 2020), potentially leading to suppressed response to vaccines. Besides, a recent study reported that Me-PFOSA-AcOH may led to cardiovascular diseases by targeting toll-like receptor 4 (TLR4) (Mao et al. 2024). TLR4 is an essential part of the innate immune system and may play a role in immune response to vaccines.

Several limitations of this study should be acknowledged. First, we examined eight PFAS compounds, and thus, a few significant findings are expected merely by chance. Second, PFAS was only measured in maternal plasma samples collected within 1–3 days after delivery. Given the long half-lives, PFAS levels shortly after delivery are highly correlated with levels during pregnancy, indicating in-utero exposure (Oh et al. 2022). However, we did not measure PFAS during early childhood, which may confound the impact of in-utero exposure on child immune response to the MMR vaccine. Besides, no other persistent organic chemicals were analyzed in this study which may also affect children's immune response to vaccination. Third, VARscore, the main outcome in this study, was calculated based on IgG reactivity to multiple peptides covering each virus via PhIP-Seq. Previous studies have reported that VARscore has high concordance with traditional assays in determining sero-positivity vs sero-negativity to multiple viruses (Morgenlander et al. 2024). However, the correlation between VARscore and traditional IgG titer for either measles or rubella remains to be determined. Fourth, most of the post-vaccination children have received only one dose of vaccines, and thus, further studies are needed to verify whether similar associations were observed in children after two doses of vaccines in the same cohort. This study only examined PFAS's effect on the MMR vaccine. More studies are needed to investigate the PFAS's effect on other routine pediatric vaccines.

In summary, this present study suggests that maternal PFAS exposure is associated with reduced antibody response to the measles vaccine in children, and such association is more pronounced in preterm infants and in Black children. The findings highlight the need for further research to replicate these results and elucidate the underlying mechanisms at play. If the associations are confirmed, it would be important to implement public health strategies aimed at reducing PFAS exposure and optimizing MMR vaccination. From public health perspective, even small shifts in immune function at the population level (decreased antibody reactivity) could have significant implications for the effectiveness of vaccination programs and the risk of measles outbreaks.

Author contributions

Xiumei Hong: Conceptualization, Investigation; Formal analysis, Writing – original draft,Visualization; William R. Morgenlander: Data curation, Writing – review and editing; Kari Nadeau: Visualization,

Writing – review and editing; Guoying Wang: Data curation, Writing – review and editing. Pamela Frischmeyer: Visualization, Writing – review and editing; Colleen Pearson: Data curation; Resource; William G. Adams: Data curation; Resource; Hongkai Ji: Funding acquisition, Supervision, Writing – review and editing; Benjamin Larman: Funding acquisition, Supervision, Writing – review and editing. Wang, Xiaobin: Conceptualization, Funding acquisition, Supervision, Project administration, Writing – review and editing. All the authors provided critical review and approval of this manuscript.

Data availability statement

Data will be made available upon reasonable request and after institutional IRB review and approval.

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CRediT authorship contribution statement

Xiumei Hong: Writing – original draft, Visualization, Investigation, Formal analysis. **William R. Morgenlander:** Writing – review & editing, Data curation. **Kari Nadeau:** Writing – review & editing, Visualization. **Guoying Wang:** Writing – review & editing, Data curation. **Pamela A. Frischmeyer-Guerrerio:** Writing – review & editing, Visualization, Conceptualization. **Colleen Pearson:** Writing – review & editing, Resources, Data curation. **William G. Adams:** Resources, Data curation. **Hongkai Ji:** Writing – review & editing, Supervision, Funding acquisition. **H. Benjamin Larman:** Writing – review & editing, Supervision, Funding acquisition. **Xiaobin Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [H.B.L. is a founder of Infinity Bio, a provider of antibody reactome profiling services. All other authors have no conflicts to disclose].

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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.2025.109433.

Data availability

Data will be made available on request.

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