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Association between serum per- and polyfluoroalkyl substances concentrations and common cold among children and adolescents in the United States

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Abstract

Background: Per- and polyfluoroalkyl substances (PFAS) exert immunosuppressive effects in experimental animals. Few epidemiologic studies investigated PFAS exposure and immune-related clinical outcomes such as common cold, especially during childhood when the immune system is developing.

Methods: This study used data from the National Health and Nutrition Examination Survey and included 517 children 3–11 years (2013–2014 cycle) and 2732 adolescents 12–19 years (2003–2016 cycles). Serum concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic

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Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107239.

acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) were quantified. Common cold was self-reported by the participant or parent as having a head cold or chest cold in the last month. Multivariable logistic regression models were applied to examine the covariate-adjusted odds ratios (ORs) between individual PFAS concentrations and common cold incidence in the past month. The joint effect of PFAS mixtures was evaluated using Probit Bayesian Kernel Machine Regression (BKMR).

Results: A doubling of serum PFHxS concentration was associated with a 31% higher odds (OR = 1.31, 95% CI: 1.06, 1.62) of common cold among children. Serum PFNA (OR = 1.36, 95% CI: 0.93, 1.98) and PFOA (OR = 1.32, 95% CI: 0.67, 2.62) concentrations were also related to common cold among children, as were serum PFOS concentrations among adolescents (OR = 1.13, 95% CI: 0.96, 1.32). ORs were higher in male than female children and adolescents. BKMR showed a clear increasing trend of common cold estimates across quantiles of the total PFAS mixture concentration among children, while no obvious pattern emerged in adolescents.

Discussion: Among children in the United States, serum concentrations of PFAS mixtures, especially PFHxS and PFNA, were associated with higher odds of common cold. Among adolescents, PFOS was associated with increased common cold in the last month. This study contributes to the existing evidence supporting the immunotoxicity of PFAS in childhood and adolescence.

Keywords

PFAS; Common cold; Immunotoxicity; Children; Adolescents; U.S.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a family of highly fluorinated aliphatic compounds (Buck et al., 2011). Due to hydrophobic and oleophobic properties, PFAS have diverse commercial and industrial applications, including in the manufacturing of textiles, non-stick cookware, food packaging, furniture, and firefighting foams (Kotthoff et al., 2015). Long-chain PFAS are extremely persistent and bioaccumulate in the environment and in living organisms including humans (Conder et al., 2008). These compounds have been detected in human blood for over two decades (Hansen et al., 2001). Concern over potential health effects of PFAS exposure began in the early 2000s and led to the voluntary phase-out of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) in the industry (Land et al., 2018). Although declines in serum PFOA and PFOS concentrations following this phase-out have been reported across diverse populations worldwide (Eriksson et al., 2017; Grandjean, 2018; Harris et al., 2017; Hurley et al., 2018), these compounds are still highly detected in individuals born after the phase-out (Ye et al., 2018), due to transformation of precursors, transplacental and breastfeeding passage, and the bioaccumulation in the food web (Koponen et al., 2018; Lal et al., 2020). Moreover, human serum concentrations of PFOS and PFOA substitutes, such as perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) (Mohsin et al., 2016), have increased worldwide during the last decade (Bjerregaard-Olesen et al., 2016; Calafat et al., 2019; Centers for Disease Control and Prevention, 2019; Glynn et al., 2015; Harris et al., 2017; Kato et al., 2011; Land et al., 2018).

Children usually present higher serum concentrations of PFAS than adults (Daly et al., 2018; Graber et al., 2019; Kato et al., 2011; Mondal et al., 2012), possibly due to lower body size to surface area and intake ratios, mouthing behaviors, and maternal exposure through placenta and breastfeeding (Bennett et al., 2015; Liew et al., 2018). Studies have linked some PFAS to health outcomes in children including altered immune function (Liew et al., 2018; Rappazzo et al., 2017; Sunderland et al., 2019). Importantly, early childhood constitutes a critical window for the maturation and priming of the immune system and early immune development may have lifelong implications with respect to response to viral and other infections (Moore et al., 2006; Simon et al., 2015; Zazara and Arck, 2019). In children, common cold, which generally refers to upper respiratory illness, is the most frequent infection among the many immune-related clinical conditions experienced in childhood (Heikkinen and Järvinen, 2003). Although common cold is mostly self-limiting, it poses an enormous burden on children, families, and society, in terms of symptom suffering, healthcare utilization and pediatric consultations, and importantly absence from school, daycare, and parental workplace (Heikkinen and Järvinen, 2003; Hellgren et al., 2010; Polyzoi and Polyzois, 2017).

Numerous experimental studies have demonstrated PFAS immunotoxicity in rodents and zebrafish models (Corsini et al., 2014; National Toxicology Program, 2016). While there is some consistent epidemiologic evidence between higher prenatal and/or childhood PFAS exposure and lower antibody levels to vaccines in children and adolescents (Fenton et al., 2020; Liew et al., 2018; Schrenk et al., 2020), findings on PFAS and other immune-related outcomes (e.g. childhood respiratory infection) are inconclusive, with differences in study design regarding both the timing of exposure and the outcome assessed (Rappazzo et al., 2017). Indeed, most studies measured PFAS exposure during gestation and investigated respiratory infections incidence in early childhood (Goudarzi et al., 2017; Impinen et al., 2018; Impinen et al., 2019; Timmermann et al., 2020). Although prospective mother-child cohorts can establish the temporal order of exposure and outcome, prenatal exposure may not reflect that of childhood, underlying the need to also evaluate childhood and adolescent exposure to PFAS. To date, only one study in Norway examined PFAS exposure in childhood in relation to airway infection among adolescents aged 16 years. This study reported generally negative associations between selected PFAS and common cold incidence (Kvalem et al., 2020). No study has investigated the association between childhood PFAS concentrations and immune-related outcomes in young children. Moreover, few studies evaluated the joint effect of PFAS mixtures on immune outcomes despite the fact that humans are exposed to complex mixtures of perfluorinated compounds in real world scenarios (Oulhote et al., 2017).

In this study, we aimed to evaluate the individual and joint associations of four serum PFAS concentrations in relation to self-reported common cold in the last month among children aged 3–11 years and adolescents aged 12–19 years in the National Health and Nutrition Examination Survey (NHANES) in the United States (U.S.).

2. Methods

2.1. Population

The study leveraged cross-sectional data from the NHANES, a national survey that aims to measure the health and nutritional status of the U.S. general population every two years. NHANES participation involves questionnaire interview, physical examination, and specimen collection for environmental and biomarker measurements. Detailed study procedures were described by the Centers for Diseases Control and Prevention (CDC) (Centers for Disease Control and Prevention). The current analysis included 517 children aged 3–11 from the 2013–2014 cycle, which is the only cycle where PFAS concentrations were quantified for this age group (Ye et al., 2018), and 2732 adolescents aged 12–19 from 2003 to 2016 NHANES cycles.

2.2. Exposure measurement

PFAS concentrations were measured in serum from random subsamples (1/3 of the total population in that age group of the cycle) for children (3–11 years) and adolescents (12–19 years). Online solid-phase extraction coupled to high-performance liquid chromatography–isotope dilution–tandem mass spectrometry (on-line SPE-HPLC–MS/MS) was used to quantify serum PFAS concentrations. The analytical measurements followed strict quality control/quality assurance of Clinical Laboratory Improvement Amendments (CLIA) guidelines. We included measurements of four highly persistent and detected PFAS compounds, including PFOA, PFOS, PFHxS, and PFNA, which have also been shown to have the highest potential for immune effects (Schrenk et al., 2020). In cycles from 2003 to 2012, PFOA and PFOS were measured as the total concentration in serum, while cycles 2013–2014 and 2015–2016 measured the isomers of PFOA and PFOS, including linear PFOA (n-PFOA), sum of branched isomers of PFOA (Sb-PFOA), linear PFOS (n-PFOS), and the sum of monomethyl branched isomers of PFOS (Sm-PFOS). For the two cycles, we calculated concentrations of PFOA and PFOS as the sum concentration of n-PFOA and Sb-PFOA, and the sum of n-PFOS and Sm-PFOS, respectively. Table S1 shows the limits of detection (LODs) for the examined PFAS compounds over the cycles. Values below the LOD were imputed by the LOD divided by the square root of 2 (Hornung and Reed, 1990).

2.3. Outcome and covariates

Common cold was determined by the following binary question included in the '*Current Health Status Questionnaire':* "Did you/surveyed participant have a head cold or chest cold that started during the previous 30 days?". Baseline demographic data were abstracted from self-reported/parent-reported questionnaires, and included age (continuous), sex (dichotomous), race (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), and income-to-poverty ratio (<1,1≤ <2, 2 ≤). The income-to-poverty ratio is the ratio of family income to poverty guidelines. Anthropometric measures were collected by trained health technicians. Body mass index (BMI) was calculated as weight in Kg divided by height in meters squared. To assess environmental tobacco smoke exposure, serum cotinine concentration (ng/ml) was measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric (ID HPLC-APCI MS/MS) method. Children and adolescents with serum cotinine concentrations

higher than 10 ng/ml were considered as exposed to tobacco smoke (Kim, 2016). For participants in cycles 2005–2016, information on seafood, including shellfish and fish intake during the past 30 days, was collected by dietary interview.

2.4. Statistical analyses

In analyses, we accounted for the complex survey design and clustering of the data, and used the subsample population weights to produce estimates that are representative of the U.S. population, as per NHANES protocol (Chen et al., 2018). Serum PFAS concentrations were log-2 transformed to minimize the influence of outliers. We calculated descriptive statistics for participants characteristics and PFAS concentrations. Spearman correlation coefficients between log-2 transformed PFAS concentrations were calculated.

Multivariable logistic regression models were fit to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of common cold per doubling of individual PFAS concentrations after accounting for the survey design as described above. We also fit mutually adjusted logistic regression models, which included all four PFAS compounds in the same model to account for co-exposure confounding. Covariates were selected based on previous knowledge of the causal structure using Directed Acyclic Graph (DAG) and included age, sex, race, and income-to-poverty ratio (Figure S1). For models among adolescents where we used pooled data from seven cycles, we additionally adjusted for survey year (categorical variable) to control for confounding by time. We furthermore stratified analyses by participant sex to explore potential effect modification.

We further used Probit Bayesian Kernel Machine Regression (BKMR) to assess the joint effect of the total PFAS mixture on common cold. BKMR can flexibly account for correlations, non-linear associations, and interactions within the mixture (Bobb et al., 2015). The model uses Posterior Inclusion Probabilities (PIP) to estimate the relative contribution of each individual PFAS compound within the mixture on the effect on the outcome. The BKMR analyses estimate the dose-response relationships between each PFAS compound and common cold, holding the other mixture components at their median concentrations; and the joint effect of the mixture on common cold by comparing the estimate for common cold per 5th percentile increase/decrease from the median concentration (reference) of the total PFAS mixture. We used default prior parameters in the “bkmr” package (version 0.2.0) and fitted Markov Chain Monte Carlo (MCMC) chain with 10,000 iterations (Bobb, 2017). SAS survey procedure was used for the weighted analyses, and “table” and “domain” statements in the procedure were used for stratified analyses in SAS version 9.4 (SAS Institute Inc). The package “bkmr” was used in R 4.0.3 (R Development Core Team, 2020).

2.5. Sensitivity analyses

To explore the non-linear relationships between PFAS and common cold, we fit models for tertiles of PFAS concentrations among each age group. Since seafood consumption is both a source of PFAS exposure and provides beneficial nutrients for the immune system, we additionally adjusted for self/parent-reported seafood consumption in the past 30 days (Yes vs. No). Because seasonality is considered as a strong predictor of common cold, we further adjusted our analyses by the dichotomous seasonality of data collection (November

1 - April 30 vs. May 1 through October 31). We also assessed the robustness of our results by adjusting for BMI. Considering the strong associations between smoking, environmental tobacco smoke, and respiratory health (Jayes et al., 2016; Mannino et al., 2001), we adjusted for continuous serum cotinine concentrations in the analyses.

To examine the association between serum PFAS concentrations and infections more generally, we broadened our common cold outcome and additionally included flu, pneumonia, and ear infections in the past month. We fit multivariable logistic regression models to calculate the ORs and 95% CIs for overall infections per doubling of the individual PFAS concentrations adjusting for our baseline *a priori* covariates. Additionally, since asthma could be mistaken for common cold symptoms by parents, we excluded children and adolescents who self/parent-reported being told they have asthma by a doctor or a health professional.

To assess the magnitude of unmeasured confounding that could potentially fully explain the statistically significant results, we calculated E-values for the adjusted point estimates and the 95% confidence intervals closest to 1. The E-value is the minimum magnitude of the association for the unmeasured confounding in relation to both exposure and outcome on the risk ratio scale, that could fully explain away the observed covariate-adjusted results. Details for the calculation of the E-values were described previously (VanderWeele and Ding, 2017).

3. Results

3.1. Population

A total of 517 children aged 3–11 years and 2732 adolescents aged 12–19 years with complete data for the exposure, outcome, and covariates were included in the analyses (Table 1). The mean ages (SE) were 7.1 (0.1) and 15.4 (0.1) years among children and adolescents, respectively. For both age groups, more than half of the sample was non-Hispanic white (weighted percentages: 52.5% for children; 59.6% for adolescents). The prevalence of common cold in the last month was 22.7% for children and 18.3% for adolescents. Prevalence of flu, pneumonia, or ear infection in the past month was 3.7% and 3.9% for children and adolescents, respectively. No substantial differences were found in covariate characteristics comparing common cold cases to non-cases, except for past infections (flu, pneumonia, or ear infection) that showed a higher prevalence in common cold cases than non-cases in both children and adolescents.

3.2. Exposure

The examined PFAS concentrations were detected in almost all serum samples included in the study, except for Sb-PFOA (Table S1). Sb-PFOA had a low detection rate of 24.18% for children and 13.99% for adolescents. Adolescents generally had higher serum PFAS concentrations than children which could be due to higher PFAS exposure in participants from earlier NHANES cycles (Table S1). Moderate to high correlations were observed for serum PFAS concentrations (rho = 0.28–0.63 for children; rho = 0.30–0.80 for adolescents) (Figure S2).

3.3. PFAS and common cold

A doubling of serum PFHxS concentration was associated with a 31% higher odds of common cold among children (OR = 1.31, 95% CI: 1.05, 1.63). In children, serum PFNA (OR = 1.36, 95% CI: 0.93, 1.98) and PFOA (OR = 1.32, 95% CI: 0.67, 2.62) concentrations were also related to common cold although confidence intervals were wide. Among adolescents, serum PFOS concentrations showed a positive relationship with the study outcome (OR = 1.13, 95% CI: 0.96, 1.32) with limited precision. No association was seen for PFOS and common cold among children, and between PFOA, PFHxS, or PFNA with common cold among adolescents (Table 2).

3.4. Sex-stratified analyses

In sex-stratified analyses, positive associations between PFHxS concentrations and common cold were seen only among male (OR: 1.61, 95% CI: 1.18, 2.21) but not female children (OR = 0.96, 95% CI: 0.65, 1.41) (test of heterogeneity p value = 0.15) (Table 3). Similarly, positive associations between PFOS concentrations and common cold were more apparent among male adolescents (OR: 1.22, 95% CI: 0.98, 1.52) than females (OR: 1.04, 95% CI: 0.84, 1.28) (test of heterogeneity p value = 0.47). We also found a negative association for PFNA concentrations only among male adolescents (test of heterogeneity p value = 0.34). No other meaningful sex-specific associations were seen in either age group (Table 3).

3.5. PFAS mixture

In the mutually adjusted models of four PFAS compounds among children, PFHxS (OR = 1.47, 95% CI: 1.09, 2.00) and PFNA (OR = 1.36, 95% CI: 0.91, 2.04) concentrations were positively associated with common cold, while a negative association was found for PFOS (OR = 0.63, 95% CI: 0.41, 0.99). For adolescents, the mutually adjusted models showed significant positive associations between PFOS concentrations and common cold (OR = 1.26, 95% CI: 1.01, 1.56), and negative associations for both PFHxS (OR = 0.93, 95% CI: 0.84, 1.04) and PFNA (OR = 0.86, 95% CI: 0.72, 1.04) concentrations in relation to common cold (Table 2).

BKMR models showed high PIPs for PFNA and PFOA in the mixture for both children and adolescents (Table S2). Dose-response associations in BKMR models confirmed results from the single-chemical analyses and mutually adjusted models in children (Fig. 1). Among children, positive dose-response associations were found for PFOA and PFHxS in relation to common cold estimates, holding the remaining PFAS mixture components at their median concentrations. A non-linear positive dose-response association was also found for serum PFNA concentrations and common cold estimate, while a downward trend was seen for PFOS in children (Fig. 1). When the total joint PFAS mixture was considered in children, a significant increase in odds of common cold was seen per 5th percentile increase from the median concentration to the 75th percentile (Fig. 2). Specifically, the odds ratio (credible interval) of common cold was 1.23 (1.07, 1.41) comparing the 75th percentile to the median concentration of the total mixture. For adolescents, no dose-response associations were seen for any examined PFAS (Fig. 1). There was no apparent pattern of a total joint mixture effect on common cold among adolescents (Fig. 2).

3.6. Sensitivity analyses

Tertile analyses showed a dose-response relationship between PFHxS and common cold among children (Table S4). Compared to the first tertile of PFHxS concentrations, second and third tertiles were associated with 1.48 (95% CI: 0.63, 3.46) and 2.06 (95% CI: 1.09, 3.89) times odds of common cold, respectively. No other dose-response or non-linear relationships were seen (Table S4). Further adjustment for seafood consumption, seasonality, BMI, or serum cotinine concentrations did not materially change the results of our primary analyses (Tables S5–S8), with the exception of PFOA, that showed a positive direction of association with common cold among adolescents after adjusting for seafood consumption (OR = 1.12, 95% CI: 0.90, 1.38) (Table S5).

Associations between PFAS concentrations and the broadened outcome (overall infections additionally including flu, pneumonia, ear infection) were similar to the primary results with common cold as the outcome, with only a small number of additional cases added to this analysis (Table S9). After excluding participants who self-reported having asthma, the associations for children remained unchanged, while the positive association between PFOS and common cold in adolescents was strengthened (OR = 1.27, 95% CI: 1.06, 1.52) (Table S10).

For an unmeasured confounding factor to fully explain away the observed covariate-adjusted associations between PFHxS and common cold among children, the theoretical factor would need to have a risk ratio of at least 1.85 with both PFHxS exposure and common cold in order to reduce the point estimate to null, or at least a risk ratio of 1.39 to shift the confidence interval to include the null value. Similarly, an unmeasured confounding factor that is associated with both exposure and outcome by a risk ratio of 1.61 could fully explain away the observed covariate-adjusted OR between PFNA and common cold among children, while weaker confounding could not. For adolescents, the magnitude of the unmeasured confounding would need to be at least 1.32 on the risk ratio scale to fully explain away the observed point estimate between PFOS and common cold.

4. Discussion

In this nationally representative cross-sectional study of children and adolescents from the United States, higher serum PFHxS and PFNA concentrations in children were associated with higher odds of common cold in the past month using both single-chemical and multi-pollutant mixture analyses. We also reported suggestive associations between higher serum PFNA concentrations and higher odds of common cold for children, and between higher serum PFOS concentrations and higher odds of common cold for adolescents. Results may be sex-specific with males potentially being at higher risk. There was indication of positive associations between serum PFOA concentrations and common cold in children, although confidence intervals were imprecise. BKMR models showed a clear increasing trend of common cold estimates across quantiles of the total PFAS mixture concentration among children, while no clear pattern was found for adolescents.

Our findings for PFHxS, PFNA, and PFOA concentrations and common cold among children, and PFOS among adolescents are consistent with previous studies examining

prenatal PFAS exposure and common cold (Granum et al., 2013; Wang et al., 2022). A subcohort from the prospective Norwegian Mother and Child Cohort (MoBa) Study with 99 participants showed that maternal PFHxS, PFNA, and PFOA concentrations at delivery were positively associated with the number of common cold episodes by the age 3, although the association for PFHxS was imprecise likely due to the small sample size (Granum et al., 2013). A study in China with 239 mother-child pairs also found positive associations for late pregnancy serum concentrations of PFOA, PFOS, PFNA, and PFHxS in relation to common cold at age 1, although confidence intervals were imprecise (Wang et al., 2022). In contrast, a Norwegian cohort of 641 mother-child pairs reported no association between cord blood PFHxS, PFNA, and PFOA and episodes of common cold at age 2; although positive associations were found between several PFAS and the number of lower respiratory tract infection episodes from 0 to 10 years of age (Impinen et al., 2018). A major weakness of this study, however, was the limited covariate adjustment of child sex only, suggesting the possibility of unmeasured confounding bias (Impinen et al., 2018). Further, none of the three studies examined potential sex-specific effects (Granum et al., 2013; Impinen et al., 2018; Wang et al., 2022). Conversely, a separate analysis using the MoBa Study examined 2,000 Norwegian mother-child pairs and reported modest inverse associations between maternal prenatal serum PFOA and PFOS concentrations and parent-reported ever common cold by age 3 (Impinen et al., 2019). However, this study found that maternal PFAS concentrations were positively associated with other respiratory and childhood infections, including bronchitis/pneumonia, throat infection, pseudocroup and ear infection at 3 years of age (Impinen et al., 2019). Of note, this population consisted of two nested case-control studies for preeclampsia and subfecundity, which may have led to potential selection bias thereby influencing results (Impinen et al., 2019). Heterogeneity in study design regarding the timing of exposure measurement as well as outcome assessment and classification might explain the differences with our results.

Other studies found general positive trends of maternal prenatal PFAS concentrations and infectious respiratory diseases such as lower respiratory tract infection in populations from Africa, Southeast Asia, North America, and Europe (Ait Bamai et al., 2020; Bulka et al., 2021; Dalsager et al., 2016; Dalsager et al., 2021; Fei et al., 2010; Goudarzi et al., 2017; Huang et al., 2020; Manzano-Salgado et al., 2019; Timmermann et al., 2020). A study in Guinea-Bissau observed that serum PFHxS and PFOA concentrations at age 4–7 months were associated with increased odds of coughing and any morbidity, including fever, diarrhea, coughing, or vomiting by 9 months of age (Timmermann et al., 2020). This study also found that PFAS exposure was associated with increased morbidity in boys at 9 months of age, but not girls, though interaction analyses did not consistently reach statistical significance. Several studies of a cohort in Japan reported imprecise positive associations between late pregnancy plasma PFOA and PFOS concentrations and ostitis media at age of 18 months, between PFHxS and total common infectious diseases at age 4 and pneumonia at age 7, and between PFOA and pneumonia at age 7 (Ait Bamai et al., 2020; Goudarzi et al., 2017; Okada et al., 2012). Studies from the Odense Child Cohort in Denmark found that prenatal serum PFOA and PFOS concentrations were associated with increased periods of fever with co-occurrence of coughing or nasal discharge and a higher risk of lower respiratory tract infections, and prenatal PFOS concentration was associated with increased

risk of hospitalization from any infectious disease from birth to 4 years of age (Dalsager et al., 2016; Dalsager et al., 2021). Another study from the Danish National Birth Cohort including 1400 participants found positive associations between early pregnancy PFOA and PFOS concentrations and risk of hospitalization due to early childhood infections only among girls, with boys showing the opposite associations (Fei et al., 2010). A large study of 1188 mother-child dyads in Spain reported consistent negative associations between early pregnancy PFHxS concentrations and lower respiratory tract infections in toddlers, although the associations were attenuated during childhood (Manzano-Salgado et al., 2019). This study also found that higher prenatal PFOA concentrations were associated with reduced lung function at age 4 (Manzano-Salgado et al., 2019). A recent study using NHANES data observed that PFOA, PFOS, PFNA, and PFHxS concentrations and their mixtures were associated with consistently higher pathogen burden in both adults and adolescents, with associations strongest in adolescents (Bulka et al., 2021). In contrast, one study in China among 344 mother-child pairs reported no associations between the PFAS compounds examined and lower respiratory tract infection (Huang et al., 2020).

The only other study that examined serum PFAS concentrations measured in childhood (and not during pregnancy or birth) and common cold episodes was among 376 Norwegian children aged 16. The authors reported that serum PFNA and PFOS concentrations were negatively associated with common cold episodes at age 16, while no associations were found for PFHxS and PFOA (Kvalem et al., 2020). Our study reported a similar suggestive negative association for PFNA and common cold incidence in the past month among adolescents, while we also reported positive associations between adolescent PFOS concentrations and common cold. Of note, this Norwegian study similarly reported that the protective association for PFNA exposure on common cold episodes was found mostly among adolescent males and not females, which is consistent with our findings in the comparable age group (Kvalem et al., 2020). The study also reported positive associations between PFOS concentrations and lower respiratory tract infection, particularly among boys, which was consistent with our findings on PFOS and common cold. Of note, PFAS were measured in samples collected at around 2009 for this Norwegian cohort, and the serum PFOS concentrations was 5–6 times higher than the NHANES population in our study. Our finding that higher PFNA concentrations were positively associated with common cold in young children while null or slightly inverse among adolescents may suggest that children at younger ages are more susceptible to the immune-altering effects of PFAS exposure. Of note, early childhood - or the period between birth and 8 years of age - constitutes a critical window in which the immune system of the child is shaped and modulated out of the womb by the immediate real-world environment achieving a progressive maturation that will determine future health (Georgountzou and Papadopoulos, 2017; Moore et al., 2006; Simon et al., 2015; Zazara and Arck, 2019).

We found a protective association between PFOS and common cold in the mutually adjusted logistic regression models in children, which could be due to the high correlations between PFOS and the rest of PFAS compounds (correlation coefficients ranged from 0.37−0.68) (Weisskopf et al., 2018). This finding highlights the importance of using multipollutant models that can accommodate high correlations structures within chemical mixtures such as the BKMR approaches used in this study. Although BKMR also showed a negative

direction of association for PFOS and common cold in children while holding the remaining PFAS at their median concentrations, the overall association for PFAS mixture showed a clear and consistent positive dose-response with common cold. Our mixture approach is in line with opinions from international scientific committees for regulating PFAS as mixtures (Kwiatkowski et al., 2020). In their latest 2020 evaluation, the European Food Safety Authority (EFSA) selected immunotoxicity as the most critical PFAS-related health endpoint for risk assessment based on both animal and human evidence. The EFSA panel evaluated PFOA, PFOS, PFHxS, and PFNA as a mixture assuming equal potencies, and concluded that "vulnerable populations may be exposed to non-negligible immune effects, especially infants and children" (Schrenk et al., 2020). The International Federation of Gynecology and Obstetrics (FIGO) also recommended assessing PFAS as a class and called for removal of PFAS from global use in its recent 2021 statement (FIGO, 2021). Our BKMR mixture analysis results among children supported these regulatory opinions, highlighting that PFAS exposure should be conceptualized, investigated, and regulated as a mixture – or more broadly – as a class – in order to protect the most vulnerable populations, including infants and children. In support of our findings, the same long-chain PFAS compounds examined within our study have been shown to alter immune status in rodents. The observed effects were predominantly immunosuppressive, including decreased spleen and thymus weights, reduction in numbers of circulating immune cells, reduced specific antibody production, and altered cytokine regulation (Schrenk et al., 2020). Although the exact mechanisms are not elucidated, the expected mode of action of PFAS involves the Nuclear Factor Kappa B (NF-kB) signaling pathway and the upregulation of apoptotic genes in lymphoid organs (National Toxicology Program, 2016). At a molecular level, PFAS compounds showed affinity for peroxisome proliferator-activated receptors (PPARs) (Behr et al., 2020; Khazaee et al., 2021), which exert important functions in inflammation and immune responses (Christofides et al., 2021), constituting a plausible mechanism. Indirect observational data also support this possibility. For example, a study showed that prenatal PFAS exposure was associated with the expression of 52 genes related to rubella titers and/or common cold episodes measured in offspring's cord blood (Pennings et al., 2016). This gene set contained several immune-associated genes, and identified PPARδ as a toxicogenomic marker of PFAS exposure, supporting current views on PPAR- and NF-κB-mediated modes of action (Pennings et al., 2016).

A major strength of this study is the nationally representative data for U.S. children and adolescents. The exposure assessment was validated by the stringent quality control methods applied through NHANES protocols. We examined PFAS as a multi-pollutant mixture by applying state-of-the-art BKMR methodology showing consistency and coherency with our single chemical analysis and that of other studies. Our PFAS mixture findings are also in line with the opinion of regulatory agencies that PFAS should be regulated as a class (Schrenk et al., 2020). Our analysis also explored sex-specific associations, which may partially explain differences seen among previous studies. Indeed, males seemed to be at higher risk of common cold compared with females, which may be due to the known enhanced immune responsiveness to RNA viruses responsible for common cold in women (Laffont and Guéry, 2019), Furthermore, it is possible that higher excretion of PFAS through menstruation (Ding et al., 2020; Nyström et al., 2022) may result in differential exposure-

outcome scenarios for menstruating female adolescents. Future research will help to clarify the biology behind these possible differences between sexes. Additionally, we were able to conduct several sensitivity analyses which showed consistent and robust results. Admittedly, our study also has several limitations. First, the cross-sectional study design precluded us from establishing a causal relationship. However, the long half-lives (years) of the PFAS compounds examined in this study made reverse causation an improbable explanation. Second, serum PFAS concentrations were only measured in the 2013–2014 cycle for children, which limits the sample size and power to detect associations for PFOA and PFOS, since concentrations of PFOA and PFOS measured in this cross-sectional sample of U.S. children were lower compared with concentrations measured in populations from the prior decade owing to the phasing out of these compounds in the early 2000s (Ye et al., 2018). Besides, this study only examined the four most commonly investigated and persistent PFAS compounds in population. We were unable to assess other more recent short-chain and replacement PFAS compounds. Third, there might be outcome misclassification by the self-reported nature of common cold episodes in the last month. Because participants were unaware of their serum PFAS concentrations, we expect the misclassification to be nondifferential and thus would likely bias associations towards the null. Fourth, we were unable to account for breastfeeding due to lack of available data. Since breastfeeding is positively associated with neonatal (and possibly childhood) PFAS exposure (Kingsley et al., 2018) and at the same time is beneficial for neonatal and childhood health, including the immune system, confounding by breastfeeding cannot be ruled out. However, we expect that the direction of confounding by breastfeeding would trend downward, biasing our results towards the null, making our observed results conservative. Residual confounding by family socioeconomic status may have influenced our findings. Nevertheless, we calculated E-values to assess the magnitude of unmeasured confounding that would be required to explain away the results. The magnitude of E-value was relatively large (RR ranges 1.32–1.85), suggesting that unmeasured confounding would have to be relatively strong; nevertheless, such considerations should not be ruled out. Although we aimed to evaluate childhood exposure to PFAS and immune status in children, we also cannot not rule out (nor adjust for) the influence of prenatal exposure on the outcome. Future studies should try to elucidate the combined influence of prenatal and childhood exposure on immune system outcomes, which may have a long-term impact on several diseases over the lifecourse.

5. Conclusion

Serum concentrations of PFHxS and PFAS mixtures were associated with higher odds of common cold among U.S. children. PFOA was positively associated with common cold among adolescents. This study adds to the existing evidence, supporting the immunotoxicity of PFAS in childhood and adolescence. Future prospective study designs with repeated assessments are needed to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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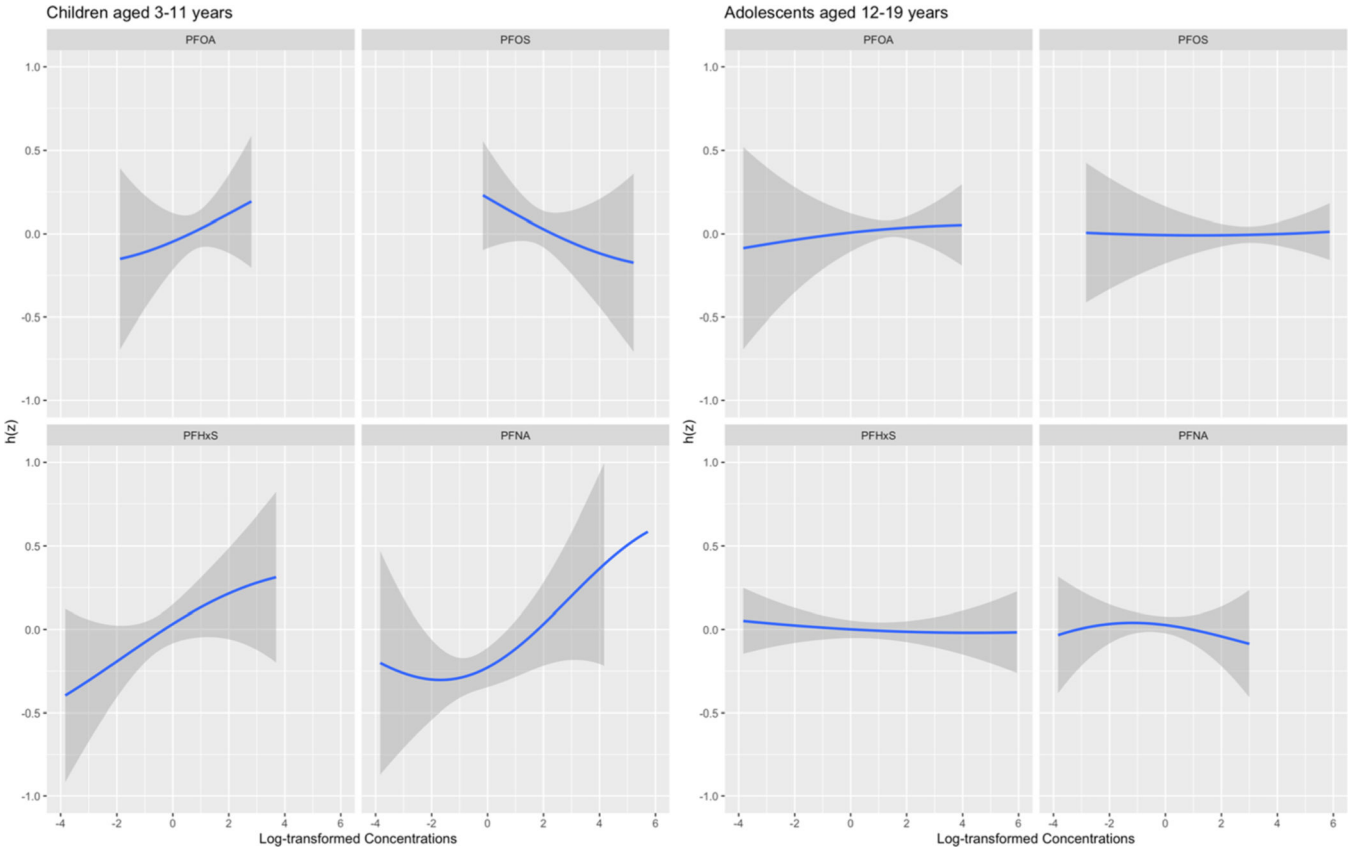

Fig. 1. Dose-response relationship between log-2 transformed individual serum per- and polyfluoroalkyl substances (PFAS) concentrations and common cold, holding the other PFAS compounds in the mixture at their median concentrations.

Note. PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid. Models were adjusted for age, sex (dichotomous), race (categorical), income-poverty ratio (categorical). Models for adolescents were additionally adjusted for survey year (categorical). The income-to-poverty ratio is the ratio of family income to poverty guidelines.

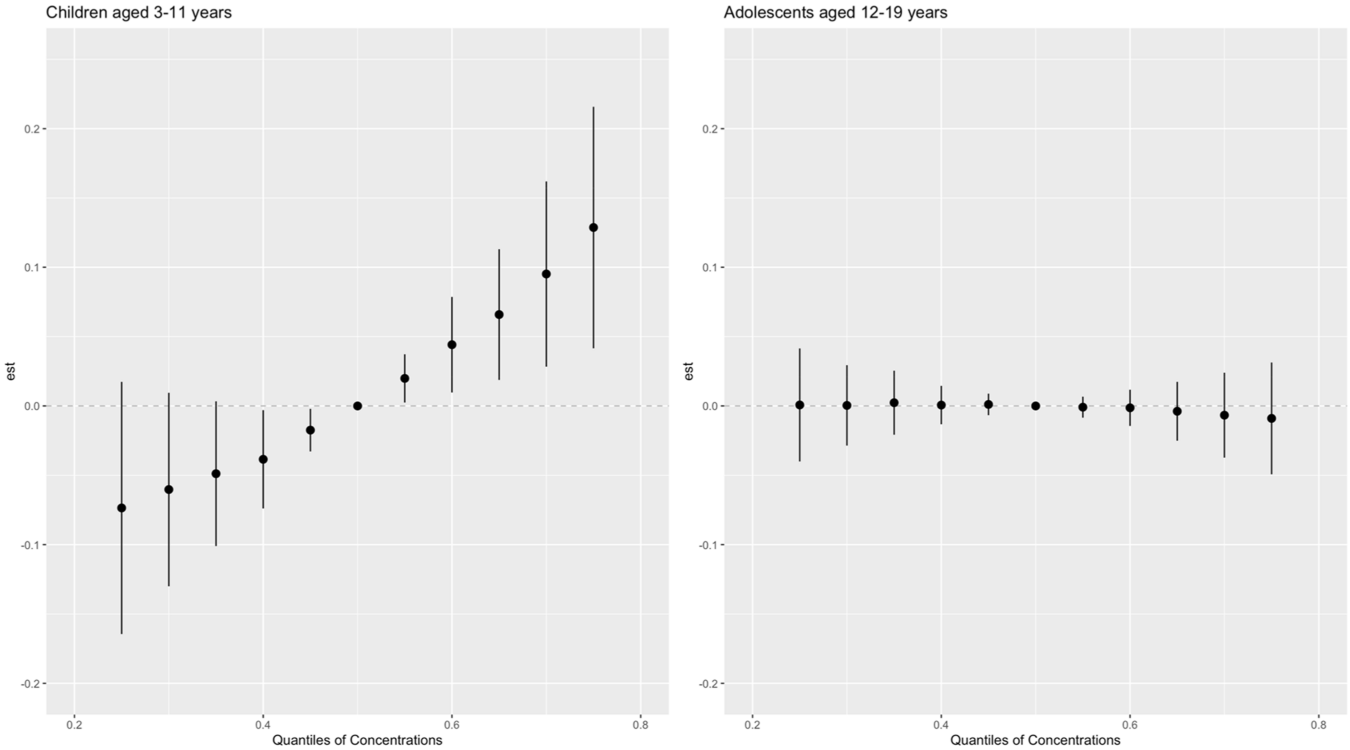

Fig. 2. Joint effect of per- and polyfluoroalkyl substances mixture on common cold among children aged 3–11 years and adolescents aged 12–19 years in the United States.

Note. Models were adjusted for age, sex (dichotomous), race (categorical), income-poverty ratio (categorical). Models for adolescents were additionally adjusted for survey year (categorical). The income-to-poverty ratio is the ratio of family income to poverty guidelines.

Table 1

Participant characteristics of children aged 3–11 years and adolescents aged 12–19 years in the United States.

Characteristics [a]	**3–11 years**			**12–19 years**		
	Total N = 517	**Common Cold Case N = 116, 22.72%**	**Non-Case N = 401, 77.28%**	**Total N = 2732**	**Common Cold Case N = 490, 18.26%**	**Non-Case N = 2242, 81.74%**
Age (year), mean ± SE	7.11 ± 0.09	6.16 ± 0.33	7.39 ± 0.16	15.44 ± 0.06	15.75 ± 0.14	15.37 ± 0.07
BMI (kg/m^2), mean ± SE	17.94 ± 0.21	17.48 ± 0.37	18.09 ± 0.25	24.14 ± 0.20	24.58 ± 0.40	24.05 ± 0.22
Male, n (%)	280 (52.22)	74 (61.70)	206 (49.43)	1462 (52.26)	245 (50.92)	1217 (52.56)
Race/Ethnicity, n (%)						
Non-Hispanic White	138 (52.49)	27 (50.77)	111 (52.99)	780 (59.62)	160 (65.22)	620 (58.37)
Non-Hispanic Black	132 (14.03)	38 (18.40)	94 (12.74)	769 (13.82)	152 (14.16)	617 (13.74)
Hispanic	178 (24.93)	39 (23.33)	139 (25.41)	958 (19.67)	153 (16.06)	805 (20.48)
Other	69 (8.55)	12 (7.50)	57 (8.86)	225 (6.89)	25 (4.56)	200 (7.41)
Income-Poverty Ratio [b], n (%)						
<1	204 (30.37)	46 (30.59)	158 (30.31)	885 (22.58)	150 (20.55)	735 (23.04)
1≤, <2	129 (19.95)	31 (23.09)	98 (19.03)	749 (21.93)	123 (22.05)	626 (21.90)
2=<	184 (49.68)	39 (46.32)	145 (50.66)	1098 (55.49)	217 (57.40)	881 (55.07)
Flu, Pneumonia, Ear infection [c], n (%)	18 (3.74)	10 (8.49)	8 (2.34)	116 (3.91)	47 (9.12)	69 (2.75)
Serum Cotinine Concentration (ng/ml), mean ± SE	0.47 ± 0.05	0.38 ± 0.11	0.39 ± 0.09	16.26 (1.70)	19.03 ± 3.63	15.64 ± 1.80
Ever Asthma, n (%)	80 (13.11)	26 (14.96)	54 (12.56)	513 (19.09)	103 (21.28)	410 (18.60)
Exposed to Tobacco Smoke [d], n (%)	1 (0.33)	0 (0)	1 (0.43)	311 (12.41)	60 (14.67)	251 (11.90)

a: Statistics were weighted by sample weights suggested by NHANES.

b: The income-to-poverty ratio is the ratio of family income to poverty guidelines.

c: Four missing observation in the 12–19 years group.

d: People with serum cotinine concentration >10 ng/ml were considered as exposed to tobacco smoke.

Table 2

Odds Ratios (95 %CI) of common cold in relation to log-2 transformed serum per- and polyfluoroalkyl substances concentrations among children aged 3–11 years and adolescents aged 12–19 years in the United States.

Biomarkers	3–11 years (N = 517)		12–19 years (N = 2732)	
	Single-chemical OR (95 %CI) [a]	Mutually adjusted OR (95 %CI) [b]	Single-chemical OR (95 %CI) [a]	Mutually adjusted OR (95 %CI) [b]
PFOA	1.32 (0.67, 2.62)	1.17 (0.51, 2.68)	1.06 (0.89, 1.27)	1.06 (0.80, 1.39)
PFOS	1.06 (0.75, 1.49)	0.63 (0.41, 0.99)	1.13 (0.96, 1.32)	1.26 (1.01, 1.56)
PFHxS	1.31 (1.05, 1.63)	1.47 (1.09, 2.00)	1.00 (0.91, 1.10)	0.93 (0.84, 1.04)
PFNA	1.36 (0.93, 1.98)	1.36 (0.91, 2.04)	0.96 (0.83, 1.10)	0.86 (0.72, 1.04)

Note: PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

a: Models were adjusted for age, sex (dichotomous), race (categorical), income-poverty ratio (categorical). Models for adolescents were additionally adjusted for survey year (categorical). The income-to-poverty ratio is the ratio of family income to poverty guidelines.

b: Models were mutually adjusted for all four PFAS compounds. Covariates included: age, sex (dichotomous), race (categorical), income-poverty ratio (categorical). Models for adolescents were additionally adjusted for survey year (categorical). The income-to-poverty ratio is the ratio of family income to poverty guidelines.

Table 3

Sex-specific Odds Ratios (95 %CI) of common cold in relation to log-2 transformed serum per- and polyfluoroalkyl substances concentrations among children aged 3–11 years and adolescents aged 12–19 years in the United States.

Biomarkers	3–11 years			12–19 years		
	Male OR (95% CI) [a]	Female OR (95% CI) [a]	Test of Heterogeneity p	Male OR (95% CI) [a]	Female OR (95% CI) [a]	Test of Heterogeneity p
PFOA	1.28 (0.59, 2.74)	1.43 (0.47, 4.41)	0.87	0.98 (0.76, 1.26)	1.12 (0.86, 1.46)	0.68
PFOS	1.03 (0.66, 1.60)	1.14 (0.62, 2.08)	0.66	1.22 (0.98, 1.52)	1.04 (0.84, 1.28)	0.47
PFHxS	1.61 (1.18, 2.21)	0.96 (0.65, 1.41)	0.15	1.07 (0.94, 1.22)	0.92 (0.80, 1.05)	0.15
PFNA	1.41 (0.86, 2.31)	1.27 (0.86, 1.89)	0.73	0.86 (0.73, 1.02)	1.05 (0.84, 1.31)	0.34

Note: number of common cold cases/sample size: children aged 3–11 years male 74/280, female 42/237; adolescents aged 12–19 years male 26/187, female 29/174. PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

[a]: Models were adjusted for age, race (categorical), income-poverty ratio (categorical). Models for adolescents were additionally adjusted for survey year (categorical). The income-to-poverty ratio is the ratio of family income to poverty guidelines.