Per- and Polyfluoroalkyl Substances and Immune Function in Children

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I have no conflicts of interest to declare.
INTRODUCTION

Works to understand how the Environment impacts reproductive health from the very earliest stages of life – from the formation of gametes and embryos – to the birth of infants and throughout child health and development.

Our mission is to
Use cutting-edge evidence to inform clinical practice, translate science into policy action, and implement prevention strategies to improve the health of mothers, fathers, and their children.
**BACKGROUND**

**Manmade Persistent Chemicals**
- Large class of synthetic chemicals
- Persistent, long half lives (2-9 years)
- “Forever chemicals”

**Widespread Applications**
- Heat, oil, stain, and water resistant
- Diverse commercial applications
  - Textiles, non-stick cookware, food packaging, furniture, and firefighting foams
Exposure Pathways

- Dietary ingestion: packaging, seafood, drinking water
- Dust ingestion
- Dermal absorption
- Indoor air inhalation

BACKGROUND

Children have higher body burden of PFAS

- Mouthing behaviors
- Different body size to surface area and intake ratios
- Placental transfer
- Breastfeeding
Early Childhood as a Critical Window for Immune System Maturation

The immune system gradually matures throughout childhood.

Deviations during this early "training period" may have long-term consequences for immune system outcomes.


02
PFAS and Immune Function
Experimental and Epidemiologic Evidence
Experimental Studies in Rodents

Most studies focused on PFOS and PFOA.
Some studies for PFNA and PFDA
Very limited evidence for other congeners

Immunotoxic effects
- Decreased spleen and thymus weights
- Reduction in circulating immune cells
- Reduction in antibody levels
- Altered cytokine production

Mode of action
- Not elucidated,
- May involve NF-kB
- Upregulation of apoptotic genes in thymus and spleen
- Possible involvement of peroxisome proliferator-activated receptors (PPARs)

In their latest 2020 evaluation, the European Food Safety Authority (EFSA) selected immunotoxicity as the most critical health endpoint for risk assessment based on both animal and human evidence.
PFAS and Immune Function

Limitations of animal models: Relevant toxicokinetic differences between rodents and humans

Table 2b: Studies on immunological effects of PFAS in rodents

<table>
<thead>
<tr>
<th>Species</th>
<th>Strain</th>
<th>Sex</th>
<th>Route</th>
<th>Duration (days)</th>
<th>PFAS</th>
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<th>LOAEL (mg/kg per day)</th>
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Epidemiologic Evidence

- **Immunosuppression**
  - **Antibody level**: prenatal or childhood PFAS exposure is negatively associated with specific antibody levels in childhood (Most robust evidence)
  - **Other laboratory markers of the immune function**: reduced C-reactive protein response, increased basophil counts among children
  - **Immune morbidity**: increased risks of common cold, infections, upper and lower respiratory airway infections among children

- **Immunoreactivity**
  - Some evidence suggesting association between PFAS and asthma, allergy, serum IgE levels
PFAS AND COMMON COLD in NHANES

Methods and Results

National Health and Nutrition Examination Study (NHANES)

A national survey

- Measures the health and nutritional status in the United States every two years
- Involves questionnaire interview, physical examination, and specimen collection for environmental and biomarker measurements

We included children aged 3 to 11 and adolescents aged 12-19 from the 2013-2014 cycle

- 1/3 of the total number of children or adolescents in the cycle
- 2013-2014 is the only cycle where PFAS were measured in children aged 3-11 years
Exposure
Serum concentrations of the following PFAS compounds: PFOA, PFOS, perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA)

Outcome
Common cold obtained by: “Did your child have a head cold or chest cold that started during the previous 30 days?”

Covariates
Age (continuous), sex (dichotomous), races (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), and income-poverty ratio (<1, <1< and <2, 2=<) which is the ratio of family income to poverty guidelines

Obtained from questionnaires

Statistical Analysis
Multivariable logistic regression to estimate odds ratio (OR) and 95% confidence interval (CI) of common cold per doubling of the individual PFAS biomarker concentration, adjusting for covariates

Weighted by NHANES sampling weights

Further investigated effect modification by sex
Probit Bayesian Kernel Machine Regression (BKMR): To assess the joint effect of the PFAS mixture on common cold.

BKMR can account for correlations, non-linear associations and interactions within mixture.

Allowed us to evaluate:
1) Individual dose-response relationships between each compound and common cold when holding other compounds in the mixture at their median concentrations.

2) Joint effect of the mixture on common cold by comparing the estimate for common cold across quantiles of the total mixture PFAS concentrations to the estimate in the median concentration of total mixture.

Children 3-11 years

- N=517
- Mean age 7
- 52% non-Hispanic white
- 14% non-Hispanic black
- Prevalence of common cold 23%

Adolescents 12-19 years

- N=394
- Mean age 16
- 55% non-Hispanic white
- 15% non-Hispanic black
- Prevalence of common cold 17%
### PFAS Biomarker Distribution

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>3-11 years</th>
<th>12-19 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Detection Rate</td>
<td>GM (ng/ml)</td>
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<tr>
<td>PFOA</td>
<td>100%</td>
<td>1.90</td>
</tr>
<tr>
<td>PFOS</td>
<td>100%</td>
<td>3.87</td>
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<tr>
<td>PFHxS</td>
<td>99.81%</td>
<td>0.85</td>
</tr>
<tr>
<td>PFNA</td>
<td>99.81%</td>
<td>0.80</td>
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</table>

### Multivariate Model

**Adjusted Odds Ratio of Common Cold per Doubling of Biomarker Concentrations**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>3-11 years</th>
<th>12-19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFOA</td>
<td>1.32 (0.83, 2.10)</td>
<td>1.18 (0.71, 1.97)</td>
</tr>
<tr>
<td>PFOS</td>
<td>1.06 (0.76, 1.48)</td>
<td>1.16 (0.76, 1.78)</td>
</tr>
<tr>
<td>PFHxS</td>
<td>1.31 (1.06, 1.62)</td>
<td>1.23 (0.96, 1.59)</td>
</tr>
<tr>
<td>PFNA</td>
<td>1.36 (1.03, 1.80)</td>
<td>0.68 (0.46, 1.00)</td>
</tr>
</tbody>
</table>

**Covariates:** Age (continuous), sex (dichotomous), races (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), and income-poverty ratio (<1, 1< and ≥2, 2<), which is the ratio of family income to poverty guidelines.
## Multivariate Model
### Adjusted Odds Ratio of Common Cold per Doubling of Biomarker Concentrations

### Stratified by Sex

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Male 3-11 years (95% CI)</th>
<th>Female 3-11 years (95% CI)</th>
<th>Test of Heterogeneity p</th>
<th>Male 12-19 years (95% CI)</th>
<th>Female 12-19 years (95% CI)</th>
<th>Test of Heterogeneity p</th>
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</thead>
<tbody>
<tr>
<td>PFOA</td>
<td>1.28 (0.71, 2.29)</td>
<td>1.43 (0.63, 3.25)</td>
<td>0.84</td>
<td>0.69 (0.32, 1.50)</td>
<td>1.55 (0.77, 3.10)</td>
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<td>PFOS</td>
<td>1.03 (0.67, 1.58)</td>
<td>1.14 (0.65, 1.99)</td>
<td>0.65</td>
<td>0.76 (0.30, 1.90)</td>
<td>1.42 (0.89, 2.24)</td>
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<td>PFHxS</td>
<td><strong>1.61</strong> (1.20, 2.18)</td>
<td><strong>0.96</strong> (0.67, 1.37)</td>
<td><strong>0.09</strong></td>
<td>1.14 (0.79, 1.63)</td>
<td>1.37 (0.94, 2.02)</td>
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<td>PFNA</td>
<td>1.41 (0.99, 2.01)</td>
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<td>0.33 (0.15, 0.72)</td>
<td>0.96 (0.59, 1.56)</td>
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**Covariates:** Age (continuous), sex (dichotomous), races (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), and income-poverty ratio (<1, =1< and <2, 2=<) which is the ratio of family income to poverty guidelines.

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## BKMR Model

Univariate dose-response relationship between individual PFAS concentration and common cold estimate, holding all other PFAS concentrations at their median concentrations.
BKMR Model

Cumulative effect of the total PFAS concentration on common cold:
Change in common cold estimate per 5th percentile increase/decrease from the median concentrations of all PFAS biomarkers

3-11 years

12-19 years

SUMMARY

Robust association for serum PFHxS concentration and increased odds of common cold among children and adolescents.

Positive association between serum PFNA concentration and common cold in children while a possible negative association among adolescents.

A clear increasing trend of common cold estimate across quantiles of the concentration of the total PFAS mixture among children, but not adolescents.
Conclusions

Associations between PFAS and common cold most evident during childhood

**Early childhood may be a more critical period for PFAS-related immune effects** compared to adolescence

Adolescent PFAS exposure may be more prone to confounding by dietary, personal care product use, and other exposure sources or behaviors (e.g. smoking/alcohol)
DISCUSSION

Strengths

- Nationally representative simple
- Childhood window of exposure
- Long half-lives of PFAS counteracts cross-sectional design, making reverse causality less likely
- Common cold as a marker of general immune system function
- Mixture methodology

Limitations

- Lack of data on confounders: breastfeeding and dietary intake (e.g. seafood consumption)
- Self-reported outcome
- Inability to account for prenatal PFAS of NHANES participants
- Investigate four of the most important PFAS, exposed to dozens of congeners that were not accounted for - likely leads to underestimation of effect

PFAS Lessons: Safety must be demonstrated before commercialization


Mixtures, rather than isolated PFAS, may lead to immunosuppressive effects and increased susceptibility to common cold infections

The PFAS mixture effect was clearly evident in childhood, which represents one of the most critical windows of exposure for immune function

Although there is limited immunotoxicological data for PFNA and PFHxS, our results suggest that these perfluorinated compounds are not safer than PFOA and PFOS
ACKNOWLEDGEMENTS

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THANK YOU

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