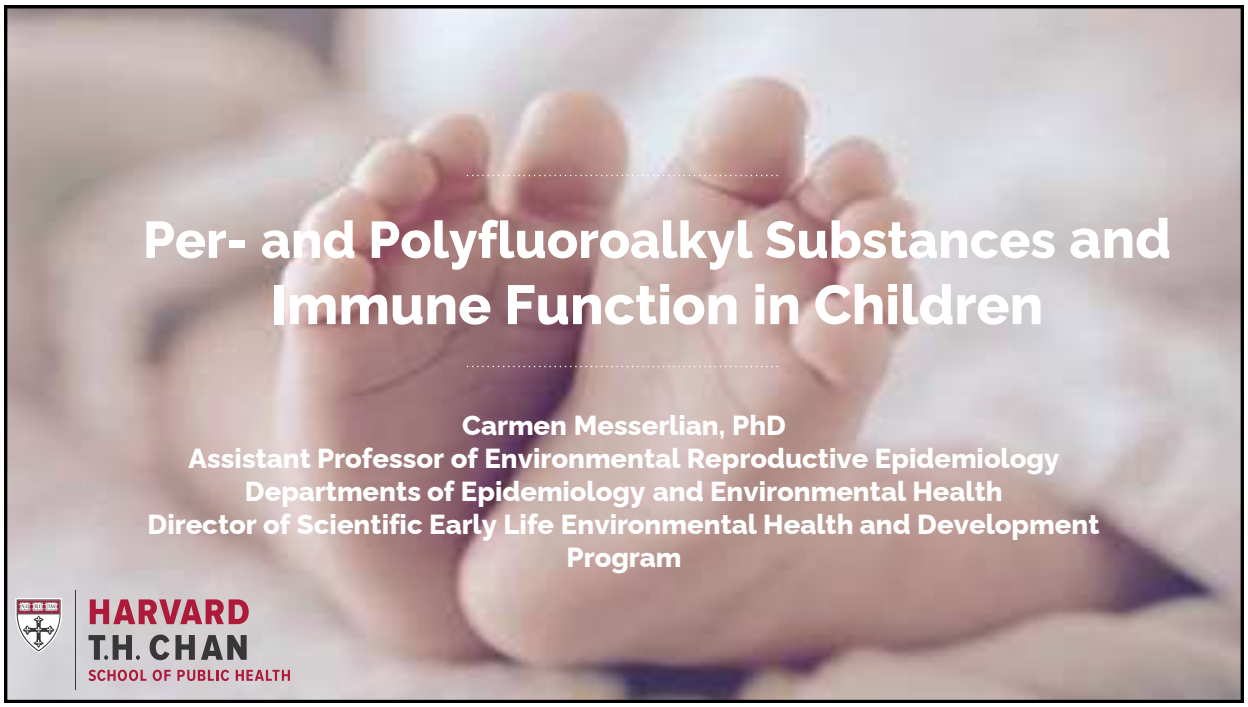

Per- and Polyfluoroalkyl Substances and Immune Function in Children

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I have no conflicts of interest to declare.

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PLAN

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PFAS AND IMMUNE FUNCTION

03
PFAS AND COMMON COLD in NHANES

04
CONCLUSIONS

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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.

SEED
Scientific Early Life Environmental Health & Development Program

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01

BACKGROUND

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BACKGROUND

Perfluoro-octanoic acid (PFOA)

Perfluoro-octane sulfonic acid (PFOS)

Perfluoro-nonanoic acid (PFNA)

Perfluoro-hexane sulfonic acid (PFHxS)

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

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BACKGROUND

Exposure Pathways

Dietary ingestion: packaging, seafood, drinking water

Dust ingestion

Dermal absorption

Indoor air inhalation

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BACKGROUND

Children have higher body burden of PFAS

Mouthing behaviors

Different body size to surface area and intake ratios

Placental transfer

Breastfeeding

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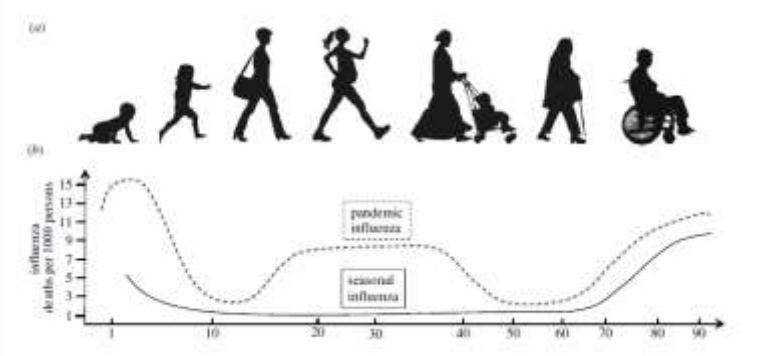
BACKGROUND

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

Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015. doi: 10.1098/rspb.2014.3085.

02

PFAS and Immune Function

Experimental and Epidemiologic Evidence

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PFAS and Immune Function

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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 involvment of peroxisome proliferator-activated receptors (PPARs)

EFSA

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.

efsa European Food Safety Authority

EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel), Schrenk et al. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J. 2020 Sep 17;18(9):e06223. doi: 10.2903/j.efsa.2020.6223.

PFAS and Immune Function

Table 20: Studies on immunological effects of PFASs in rodents

Species	Strain	Sex	Route	Duration (days)	PFAS	NOAEL (mg/kg per day)	LOAEL (mg/kg per day)	NOAEC (ng/mL)	LOAEC (ng/mL)	Immune treatment	Days before sacrifice	Immune endpoint (*)	Effect	Reference
Mouse	B6C3F1	Male	Gavage	28	PFOS	0.000166	0.00166	18	92	SRBC	5 days	PFCs	↓	Peden-Adams et al. (2008)
Mouse	B6C3F1	Female	Gavage	28	PFOS	0.00331	0.0166	123	666	SRBC	5 days	PFCs	↓	
Mouse	B6C3F1	Female	Gavage	21	PFOS	0.005	0.025	189	670	Influenza	None	Survival	↓	Guruge et al. (2009)
Mouse	B6C3F1	Male	Diet	28	PFOS	0.25	–	11,600	–	SRBC	5 days	Serum IgM, PFCs	–	Qazi et al. (2010)
Mouse	B6C3F1	Male	via dams, gavage	GD 1–17	PFOS	1	5	NR	NR	SRBC	4 days	PFCs	↓	Keil et al. (2008)
Mouse	B6C3F1	Female			PFOS	5	–	NR	–	SRBC	4 days	PFCs	–	
Mouse	C57BL/6	Male	Gavage	60	PFOS	0.00833	0.0833	674	7,132	SRBC	4 days	PFCs	↓	Dong et al. (2009)
Mouse	C57BL/6	Male	Gavage	60	PFOS	0.0167	0.0833	2,360	10,750	SRBC	7 days	Serum IgM	↓	Dong et al. (2011)
Mouse	C57BL/6	Male	Gavage	60	PFOS	0.0833	0.4167	8,210	24,530	None		TNF-α, IL-6	↑	Dong et al. (2012)
Mouse	C57BL/6	Male	Gavage	7	PFOS	–	5	–	110,460	SRBC	5 days	PFCs	↓	Zheng et al. (2009)
Mouse	C57BL/6	Male	Gavage	7	PFOS	–	5	–	97,250	None		Non-specific IgM	↓	Zheng et al. (2011)
Mouse	BALB/c	Female	Gavage	21	PFOS	–	20	–	NR	Ovalbumin	14 and 7 days (two injections)	Serum IgM	↓	Vetvicka and Vetvickova, 2013)
					PFOA	–	20	–	NR				↓	
Mouse	CD-1 (ICR)BR	Male	Gavage	29	APFO	1	10	32,000	225,000	SRBC	5 days	Serum IgM	↓	Loveless et al. (2008)
Mouse	C57BL/6	Female	Gavage	15	PFOA	1.88	3.75	NR	74,913	SRBC	5 days	Serum IgM	↓	DeWitt et al. (2008)
Mouse	C57BL/6	Female	Water	15	PFOA	7.5	30	NR	NR	SRBC	5 days	Serum IgM	↓	DeWitt et al. (2016)
Rat	SD	Male	Diet	28	PFOS	–	0.14	470	950	None		Serum IgG1	↓	Lefebvre et al. (2008)

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

PFAS and Immune Function

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

Immuno-reactivity

- Some evidence suggesting association between PFAS and asthma, allergy, serum IgE levels

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03

PFAS AND COMMON COLD in NHANES

Methods and Results

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National Health and Nutrition Examination Study (NHANES)

A national survey

Measures the health and nutritional status in the United Stated every two year

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

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Methods

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

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PFAS AND COMMON COLD in NHANES-Methods

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

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PFAS AND COMMON COLD in NHANES-Methods

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

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PFAS AND COMMON COLD in NHANES-Results

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%

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PFAS AND COMMON COLD in NHANES-Results

PFAS Biomarker Distribution

Biomarkers	3-11 years		12-19 years	
	Detection Rate	GM (ng/ml)	Detection Rate	GM (ng/ml)
PFOA	100%	1.90	100%	1.70
PFOS	100%	3.87	100%	3.62
PFHxS	99.81%	0.85	100%	1.29
PFNA	99.81%	0.80	100%	0.61

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PFAS AND COMMON COLD in NHANES-Results

Multivariate Model

Adjusted Odds Ratio of Common Cold per Doubling of Biomarker Concentrations

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

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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PFAS AND COMMON COLD in NHANES-Results

Multivariate Model

Adjusted Odds Ratio of Common Cold per Doubling of Biomarker Concentrations

Stratified by Sex

Biomarkers	3-11 years			12-19 years		
	Male	Female	Test of Heterogeneity p	Male	Female	Test of Heterogeneity p
PFOA	1.28 (0.71, 2.29)	1.43 (0.63, 3.25)	0.84	0.69 (0.32, 1.50)	1.55 (0.77, 3.10)	0.19
PFOS	1.03 (0.67, 1.58)	1.14 (0.65, 1.99)	0.65	0.76 (0.30, 1.90)	1.42 (0.89, 2.24)	0.54
PFHxS	1.61 (1.20, 2.18)	0.96 (0.67, 1.37)	**0.09**	1.14 (0.79, 1.63)	1.37 (0.94, 2.02)	0.54
PFNA	1.41 (0.99, 2.01)	1.27 (0.80, 2.01)	0.75	0.33 (0.15, 0.72)	0.96 (0.59, 1.56)	**0.03**

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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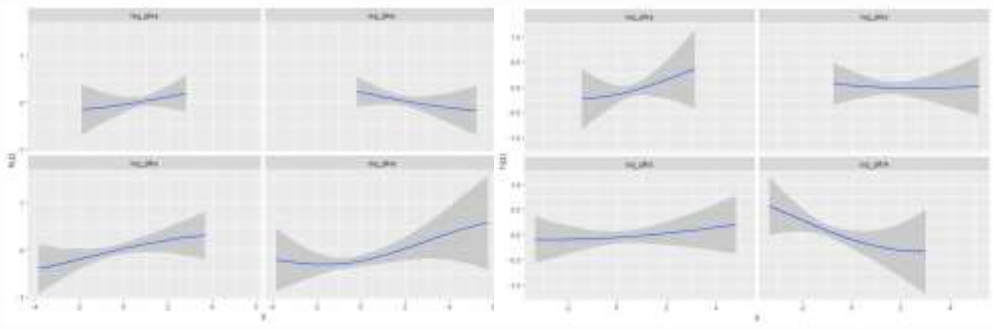
PFAS AND COMMON COLD in NHANES-Results

BKMR Model

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

3-11 years

12-19 years



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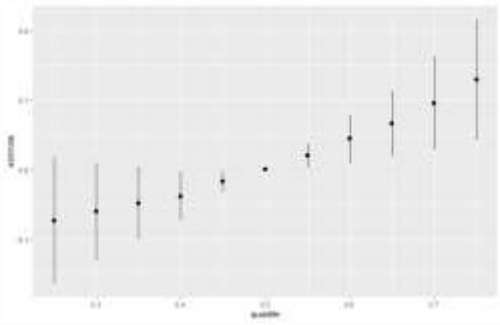
PFAS AND COMMON COLD in NHANES-Results

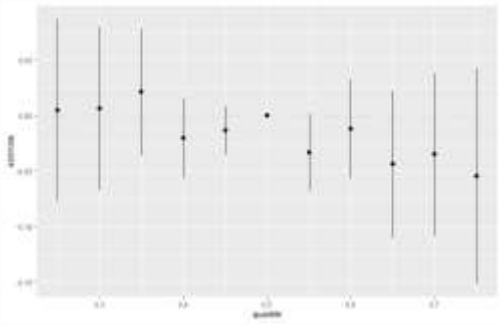
BKMR Model

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



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PFAS AND COMMON COLD in NHANES-Results

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**

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04

Conclusions

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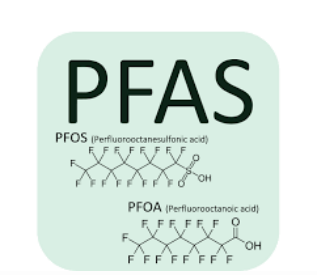
Summary



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

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

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Implications

PFAS Lessons: Safety must be demonstrated before commercialization

Grandjean P. Delayed discovery, dissemination, and decisions on intervention in environmental health: a case study on immunotoxicity of perfluorinated alkylate substances. Environ Health. 2018. doi: 10.1186/s12940-018-0405-y.

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 immunotoxilogical data for PFNA and PFHx our results suggest that these perfluorinated compounds are not safe than PFOA and PFOS

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ACKNOWLEDGEMENTS

Yu Zhang

Vicente Mustieles

Yang Sun

Yixin Wang

Stelios Vagios

Preconception PFAS Exposure and Reproduction (PREPARE) Study
R01ES031657 (PI: Messerlian)

NIEHS Program Officers

Antonia Calafat
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THANK YOU

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THRIVE