PFAS Exposure and Immune-Related Outcomes Among Children: Could Folate Mitigate the Harmful Health Impacts?

The Science of PFAS: Public Health & The Environment

April 6, 2022

Carmen Messerlian, PhD, MS, BS
Departments of Environmental Health and Epidemiology
Harvard Chan School of Public Health
Department of Obstetrics and Gynecology and Vincent Center for Reproductive Biology
Massachusetts General Hospital

NIH NIEHS

MGH 1811

SEED PROGRAM
SCIENTIFIC EARLY LIFE ENVIRONMENTAL HEALTH & DEVELOPMENT PROGRAM

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Per- and Polyfluoroalkyl Substances - Ubiquitous Exposure Across Populations

- PFAS are widely used in diverse commercial and consumer applications
- Universally detected in general population worldwide

PFAS - Altered Immune Function

Experimental Evidence

- Decreased spleen and thymus weights
- Reduced number of circulating immune cells
- Lower specific antibody production
- Altered cytokine production

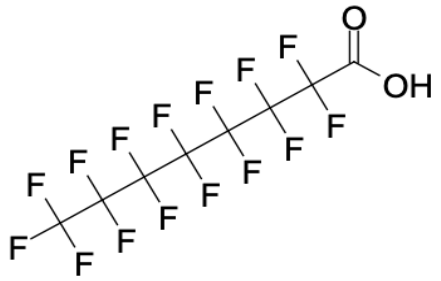
Epidemiological Evidence

- Most studies focusing on the laboratory markers of the immune function
- Negative associations on prenatal and childhood serum PFAS concentrations and diphtheria antibody levels (Faroe island cohorts)

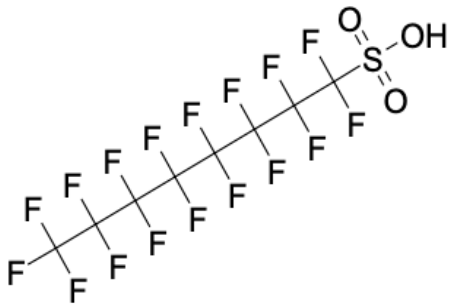
Limitations

- Insufficient and inconsistent findings on PFAS and clinical outcomes among children especially in young childhood.
- No study on mixtures

Long-chain PFAS - Persistent in Human Body

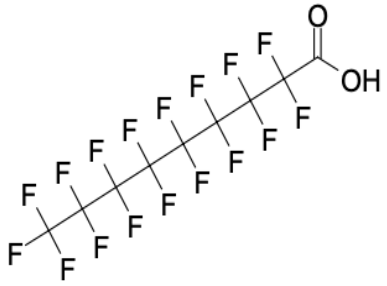


Perfluorooctanoic acid (PFOA)

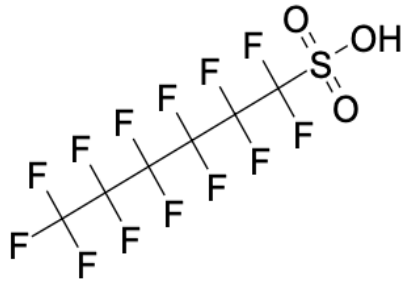


Perfluorooctane sulfonic acid (PFOS)

- Referred to as 'FOREVER CHEMICALS'
- Half-lives range from 3 years to decades



Perfluorononanoic acid (PFNA)



Perfluorohexane sulfonic acid (PFHxS)

Can Certain Nutrients Reduce PFAS Burden in Humans?

- Diets high in vegetables, fruits, grains, and beans → associated with lower PFAS concentrations in serum/plasma

Limitations

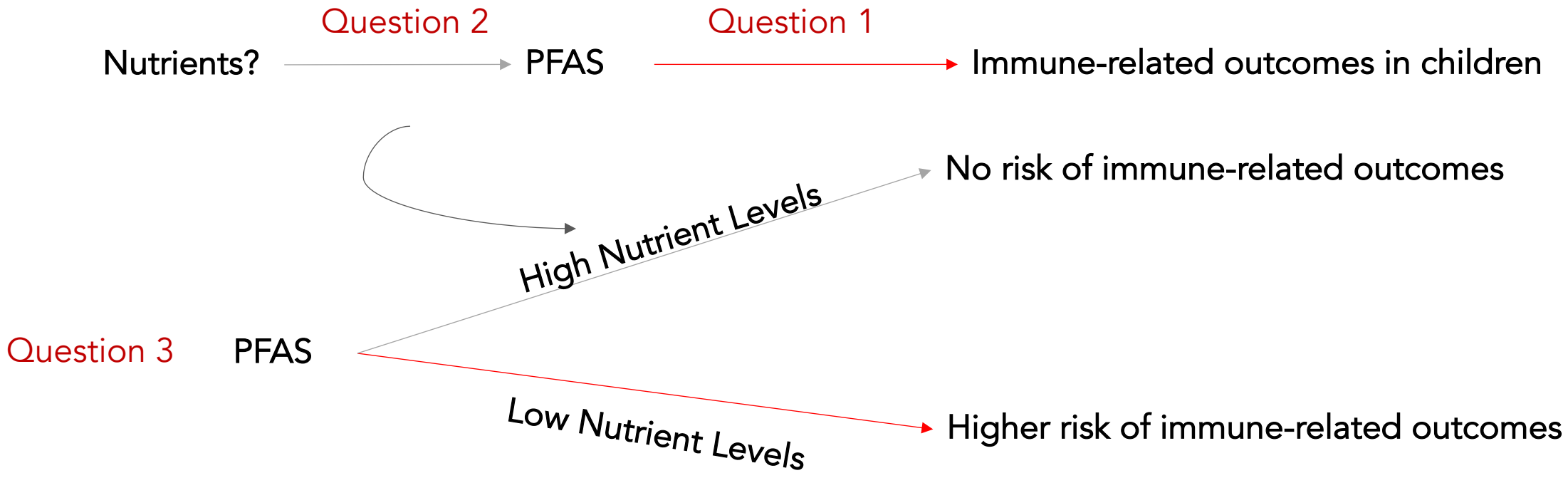
- Unclear mechanisms
- No study on specific nutrients

  → To inform interventions to reduce PFAS body burden

  → To mitigate the harmful health impacts of PFAS

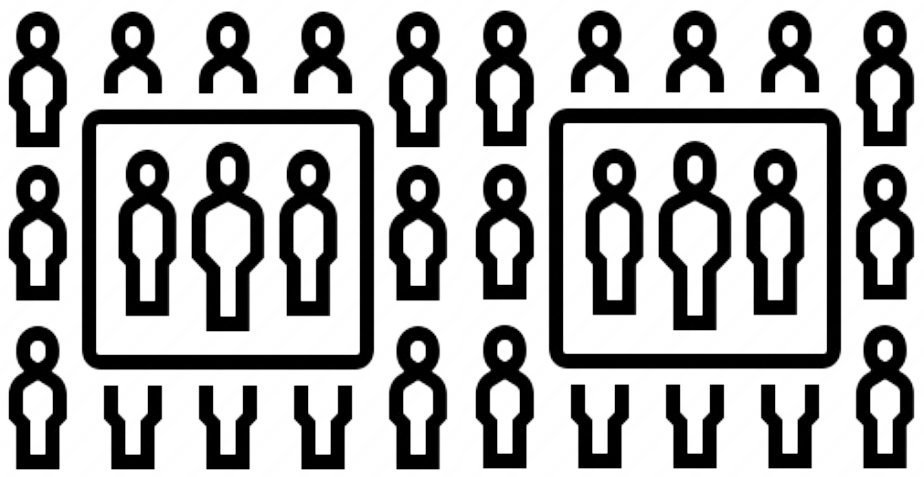
Research Questions

- ✓ Are PFAS (individual and mixtures) associated with clinical outcomes related to immune function in children?
- ✓ Can certain nutrients reduce PFAS concentrations?
- ✓ Can we identify any interactions between PFAS and nutrients on immune-related outcomes in children?



Study Design and Population

- National Health and Nutrition Examination Survey (NHANES)
- Nationally representative cross-sectional study by the Centers for Disease Control and Prevention (CDC)
- Questionnaires, physical examination and biospecimen collection



nhanes
The Nation's Mobile Health Survey

Associations of PFAS and Immune-Related Outcomes in Children?

Population

- 517 children aged 3 to 11 years and 394 adolescents aged 12 to 19 years in NHANES 2013 – 2014

Exposure

- Serum concentrations of four PFAS
  - PFOA, PFOS, PFNA and PFHxS

Outcome:

- Self/parent-reported common cold incidence in the past month
- "Did {you/Surveyed Participant} have a head cold or chest cold that started during the previous 30 days?".

Statistical analysis

- Single-chemical analysis:
  - Logistic regression modes
  - Odds Ratio (95% CI) of Common Cold per 2.7 fold increase in individual PFAS
- Mixture analysis:
  - Probit Bayesian Kernel Machine Regressions (BKMR)
  - Joint effect of the Total PFAS Mixture on common cold

Zhang et al, Under Review

Associations of PFAS and Common Colds in Children?

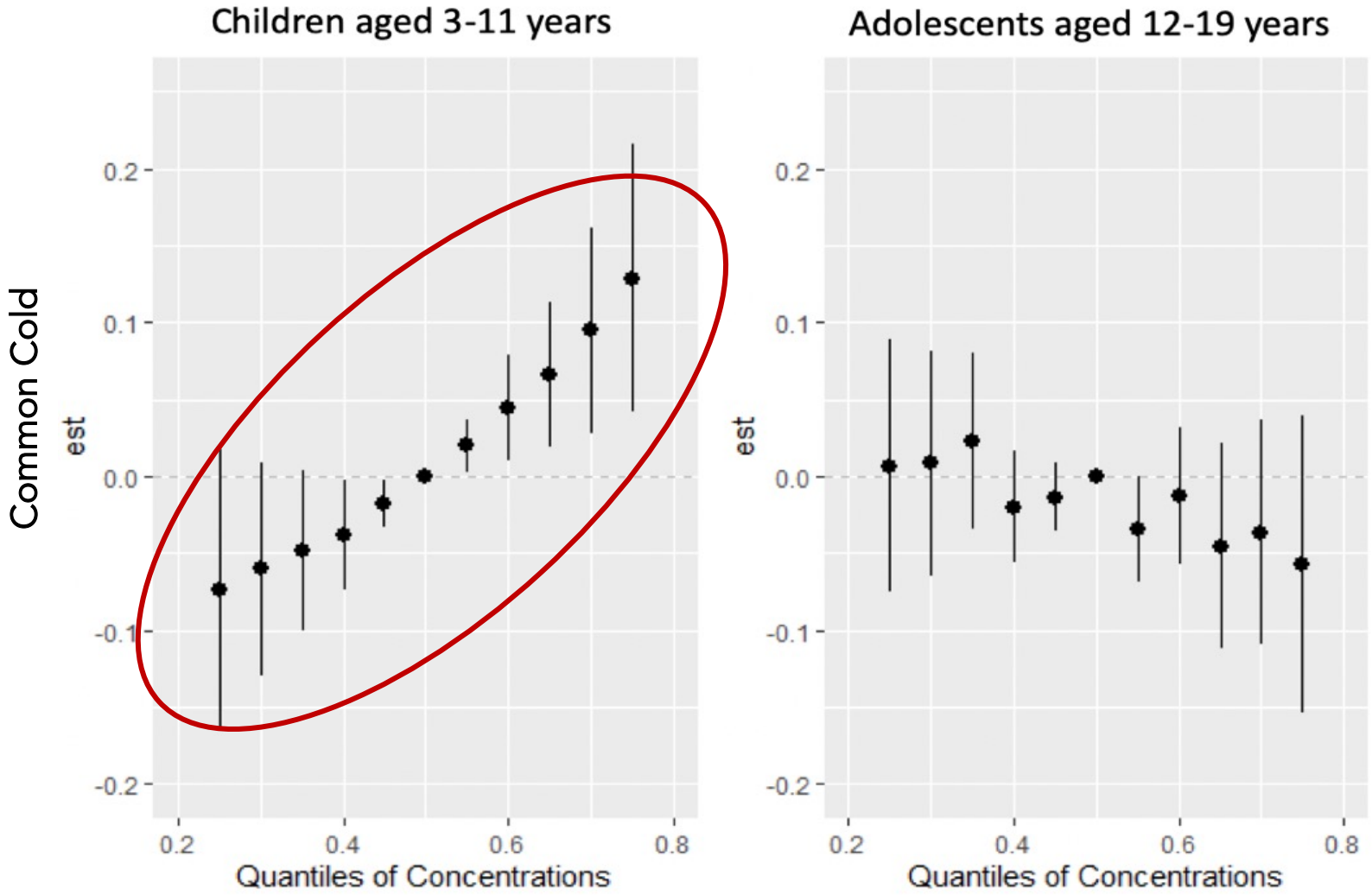
Adjusted Odds Ratios (OR) for Common Cold Per 2.7 Fold increase in PFAS Concentrations

PFAS Biomarker	Children 3-11 years OR (95%CI)	Adolescents 12-19 years OR (95%CI)
PFOA	1.32 (0.67, 2.62)	1.29 (0.70, 2.38)
PFOS	1.06 (0.75, 1.49)	1.31 (0.82, 2.09)
PFHxS	1.31 (1.05, 1.63)	1.27 (0.93, 1.72)
PFNA	1.36 (0.93, 1.98)	0.72 (0.46, 1.12)

Zhang et al, Under Review

Associations of PFAS Mixtures and Common Cold in Children?

Change in common cold estimate per 5th percentile increase or decrease
in the total PFAS mixture concentrations compared with the median total mixture concentration



Associations of PFAS and Immune-related Outcomes in Children?

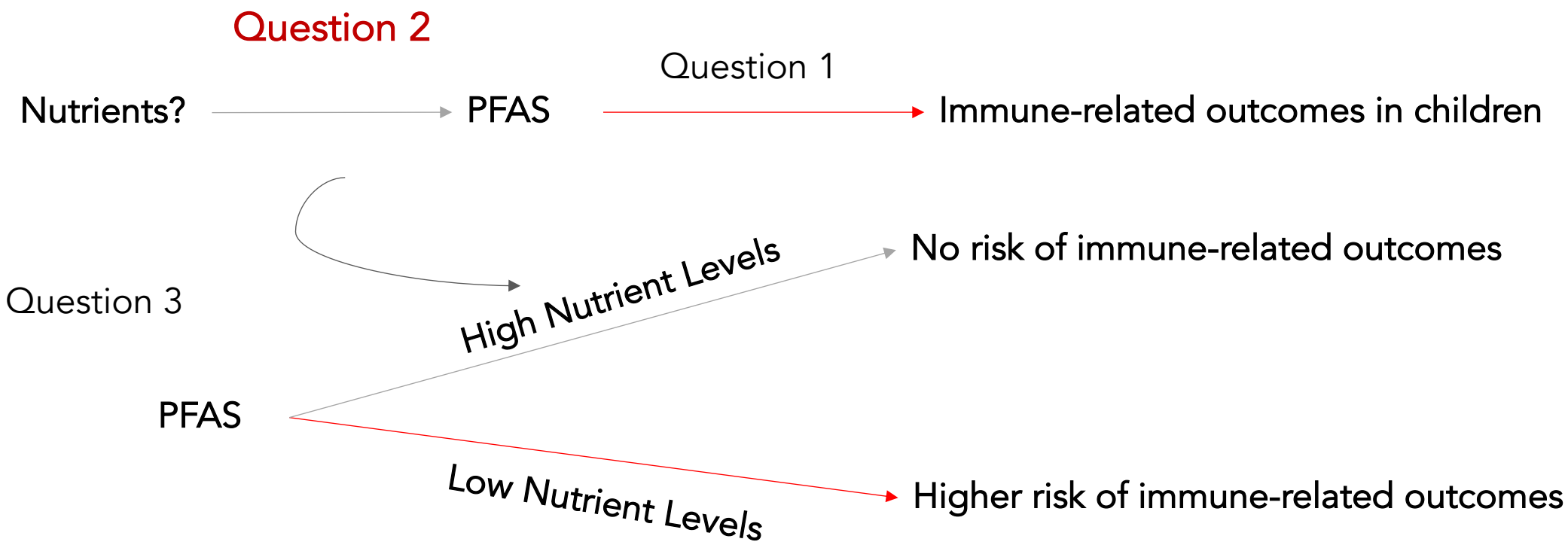
Summary

- Robust and consistent associations between higher serum PFHxS concentrations and increased odds of common cold in the past month among both children and adolescents

- Positive association between serum PFNA concentrations and common cold among children, but inverse association for adolescents

- Mixture 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 seen for adolescents

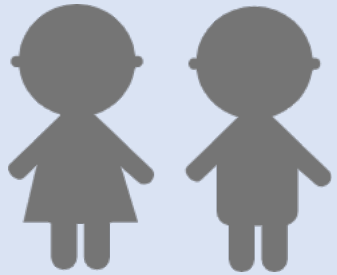
Can Nutrients Reduce PFAS Concentrations?



Can Certain Nutrients Reduce PFAS Concentrations?

Exploratory Study 1 – Experimental evidence on juice intake and reduced PFOS concentrations, Dr. Angela Slitt
Translation from bench to epidemiologic studies

Population:



NHANES 2013-2014

345 adolescents, 12-19 years

458 adults, 20-80 years

Exposure:

Pure (100%) fruit juice intake in 24h dietary recall

Outcome:

Serum concentrations of four PFAS

PFOA, PFOS, PFNA, and PFHxS

Findings:

- A 15% (95% CI: - 28%, -1%) reduction in serum PFOA concentration among adolescents who consumed pure fruit juice more than once in the past 24 hours, compared with adolescents with no intake
- No other significant differences were observed for other PFAS compounds, nor among adults

Zhang et al, ISEE 2021

Can Certain Nutrients Reduce PFAS Concentrations?

Exploratory Study 2 – Folate biomarkers in blood in relation to PFAS concentrations

Population: 2,802 adolescents and 9,159 adults NHANES, 2003 - 2016 cycles

Exposure: Folate concentrations in red blood cells (RBCs) and in serum

Outcome: Serum concentration of four PFAS compounds including PFOA, PFOS, PFNA, and PFHxS

Statistical analyses:

- Multivariable regression models
- Percent change (95% CI) of serum PFAS concentrations per 2.7-fold increase in folate biomarker
- Covariates: age, sex, race, income-to-poverty ratio, BMI, survey cycle + diet (milk and milk products, meat, poultry and fish, eggs, dry beans, peas, other legumes, nuts and seeds, grain products, fruits, vegetables)

Zhang et al, Under Review

Can Certain Nutrients Reduce PFAS Concentrations in Adolescents?

Change in PFAS concentrations in relation to 2.7 fold increase in RBC folate concentrations among Adolescents in NHANES

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	-7.34% (-16.57%, 2.91%)	-6.51% (-16.49%, 4.67%)
PFOS	**-24.36% (-33.21%, -14.34%)**	**-25.14% (-34.18%, -14.86%)**
PFHxS	**-13.00% (-21.87%, -3.12%)**	**-14.68% (-23.51%, -4.84%)**
PFNA	-12.29% (-26.12%, 4.12%)	-11.14% (-26.01%, 6.72%)

Zhang et al, Under Review

Can Certain Nutrients Reduce PFAS Concentrations in Adults?

Change in PFAS concentrations in relation to 2.7 fold increase in RBC folate concentrations among Adults in NHANES

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	**-12.45% (-17.28%, -7.35%)**	**-11.18% (-16.36%, -5.68%)**
PFOS	**-25.30% (-29.67%, -20.65%)**	**-23.54% (-28.27%, -18.49%)**
PFHxS	**-21.65% (-26.19%, -16.82%)**	**-20.47% (-25.35%, -15.27%)**
PFNA	**-11.70% (-17.32%, -5.70%)**	**-9.50% (-15.54%, -3.02%)**

Zhang et al, Under Review

Can Certain Nutrients Reduce PFAS Concentrations in Adolescents?

Change in PFAS concentrations in relation to 2.7 fold increase in serum folate concentrations among Adolescent in NHANES

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	3.82% (-2.32%, 10.34%)	5.15% (-1.25%, 11.96%)
PFOS	**-11.57% (-17.87%, -4.79%)**	**-11.11% (-17.43%, -4.30%)**
PFHxS	-1.25% (-7.14%, 5.01%)	-1.69% (-7.58%, 4.58%)
PFNA	-3.94% (-15.51%, 9.20%)	-1.67% (-14.14%, 12.60%)

Zhang et al, Under Review

Can Certain Nutrients Reduce PFAS Concentrations in Adolescents?

Change in PFAS concentrations in relation to 2.7 fold increase in serum folate concentrations among Adolescent in NHANES

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	**-5.01% (-8.35%, -1.54%)**	**-3.91% (-7.30%, -0.40%)**
PFOS	**-12.81% (-16.15%, -9.35%)**	**-10.97% (-14.40%, -7.40%)**
PFHxS	**-11.85% (-14.72%, -8.88%)**	**-10.65% (-13.65%, -7.54%)**
PFNA	-1.72% (-6.65%, 3.46%)	0.56% (-4.48%, 5.88%)

Zhang et al, Under Review

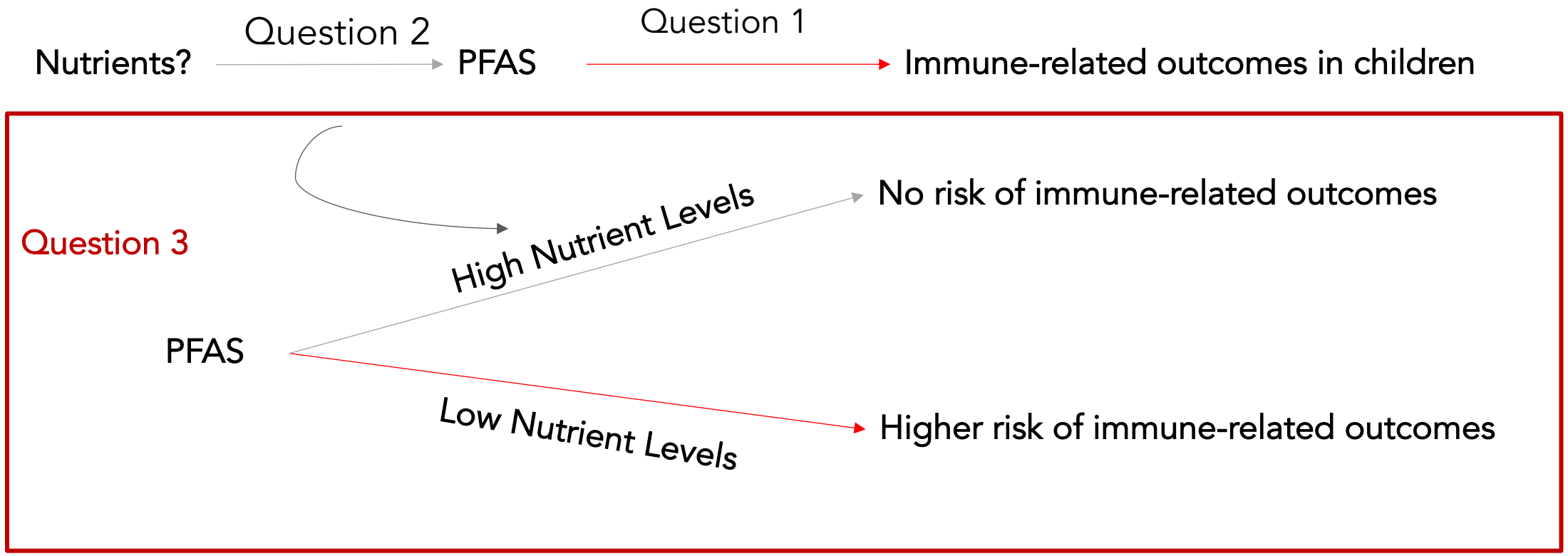
Can Certain Nutrients Reduce PFAS Concentrations in Adolescents?

Summary of NHANES Data

	Adolescents		Adults	
Biomarkers	**Folate in RBCs**	**Folate in Serum**	**Folate in RBCs**	**Folate in Serum**
PFOA	-	-	↓	↓
PFOS	↓	↓	↓	↓
PFNA	↓	-	↓	↓
PFHxS	-	-	↓	-

Zhang et al, Under Review

Can Folate Modify Associations of PFAS →Immune Outcomes?



Can Folate Modify Associations of PFAS →Immune Outcomes?

Population: N=584 adolescents

NHANES 2003-2004

Exposure: Serum concentrations of four PFAS

- PFOA, PFOS, PFNA, and PFHxS

Outcome: Blood antibody levels to measles, rubella, and varicella

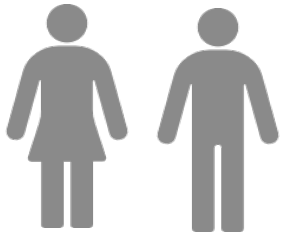
Effect Modifier: Folate concentrations in red blood cells (RBCs)

Statistical Analyses:

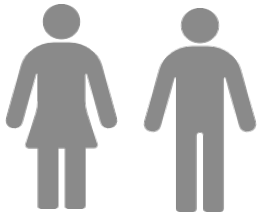
- Stratification by low vs. high folate groups
  - At median concentrations of RBCs folate 208.5 ng/ml)
- Examine PFAS → antibody associations stratified samples
  - Single chemical analysis:
    - Linear Regressions
    - % change in antibodies levels per 2.7 fold increase in individual PFAS concentrations
  - Mixture analysis:
    - Quantile G-Computation
    - BKMR

Zhang et al, In Preparation

Can Folate Modify Associations of PFAS →Immune Outcomes?

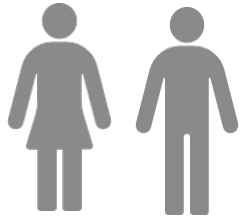


N=584
Adolescents



N=292
Low Folate Group

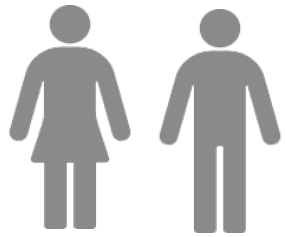
Non-Hispanic White	62.7%
Non-Hispanic Black	21.4%
Income-poverty ratio < 1	28.9%



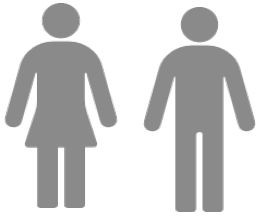
N=292
High Folate Group

Non-Hispanic White	73.0%
Non-Hispanic Black	9.0%
Income-poverty ratio < 1	22.8%

Can Folate Modify Associations of PFAS →Immune Outcomes?

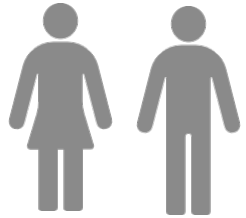


N=584
Adolescents



N=292
Low Folate Group

Seropositive proportion
Measle 98.3%
Rubella 96.3%
Varicella 95.5%



N=292
High Folate Group

Seropositive proportion
Measle 95.1%
Rubella 92.6%
Varicella 94.4%

Can Folate Modify Associations of PFAS →Immune Outcomes?

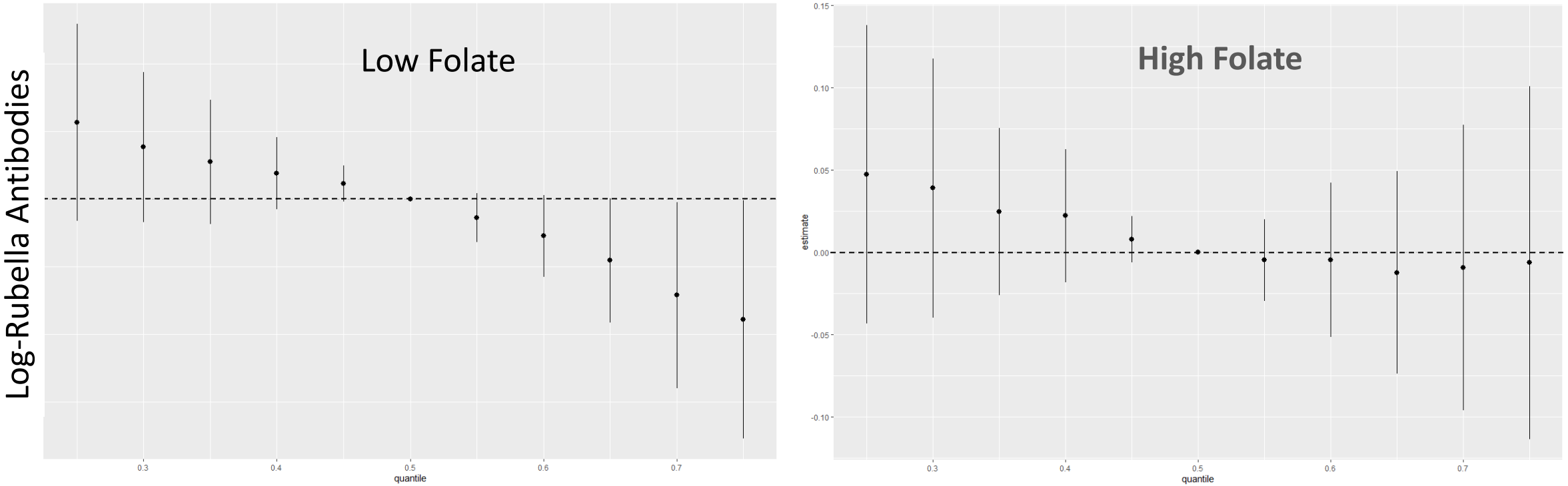
Adjusted Percent Change of Rubella Antibody per 2.7 Fold increase in PFAS Concentrations

Biomarkers	Low Folate Percent Change (95%CI)	High Folate Percent Change (95%CI)	EMM p value
PFOA	**-20.18% (-31.00%, -7.65)**	6.33% (-10.20%, 25.90%)	0.02
PFOS	**-28.56% (-38.64%, -16.82)**	2.78% (-16.00%, 25.75%)	0.003
PFHxS	**-14.40% (-23.24%, -4.55%)**	-3.09% (-15.93%, 11.71%)	0.11
PFNA	-2.37% (-19.63%, 18.60%)	19.62% (4.51%, 36.91%)	0.11
PFAS Mixtures	**-9.10% (-17.29%, -0.10%)**	-4.37% (-13.51%, 5.74%)	0.46

Zhang et al, In Preparation

Can Folate Modify Associations of PFAS →Immune Outcomes?

Change in log-Rubella Antibody per 5th percentile Increase/Decrease in Total PFAS Mixture Concentration vs. Median PFAS Concentration



Total PFAS Mixture Concentrations

Zhang et al, In Preparation

Can Folate Modify Associations of PFAS →Immune Outcomes?

Summary

- Negative associations between **PFOA, PFOS, PFHxS, and the total PFAS mixtures and rubella** antibody levels only among adolescents in the low folate group
- No associations between PFAS (individual or mixtures) and rubella antibody in the high folate group
- No associations between PFAS and measles or varicella antibody levels among adolescents

Zhang et al, In Preparation

Can Folate Modify Associations of PFAS →Immune Outcomes?

Adolescents	Low Folate			High Folate		
Biomarker	Rubella Antibody	Measle Antibody	Varicella Antibody	Rubella Antibody	Measle Antibody	Varicella Antibody
PFOA	↓	↓	-	-	-	-
PFOS	↓	-	-	-	-	-
PFHxS	↓	-	-	-	-	-
PFNA	-	↓	-	-	-	-
PFAS Mixtures	↓	-	-	-	-	-

Zhang et al, In Preparation

Potential Mechanisms

Folate and PFAS could share common transporters, including those in ATP-binding cassettes (ABC) transporter family (BCRP and MRP), and organic anion transporters (OAT)

Thus potentially decreasing the absorption of PFAS in the intestine or the reabsorption in kidney

PFAS and Folate also both bind to albumin → displacement of PFAS by folate in albumin changing renal clearance?

Limitations

Cross-sectional study design

- PFAS, folate, and immune-related outcome (common cold, antibody) measured at the same time

Window of vulnerability

- Preconception or early pregnancy PFAS and folate exposure in relation to immune outcomes in childhood

Yu Zhang, Doctoral Candidate at Harvard Chan

Grateful to Yu Zhang
Star student leading this work on
behalf of my SEED Program

SEED PROGRAM
SCIENTIFIC EARLY LIFE ENVIRONMENTAL HEALTH & DEVELOPMENT PROGRAM

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

ACKNOWLEDGEMENTS

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

NIEHS Program Officers

Centers for Disease Control and Prevention

Yu Zhang, Angela Slitt, Yxin Wang, Yang Sun, Vicente Mustieles

Vincent Center for Reproductive Biology

Massachusetts General Hospital