PFAS and Biological Aging: NHANES 2005-2012 Analysis

A Cross-Sectional Study of Per- and Polyfluoroalkyl Substances and PhenoAge

Elwood Research Team

February 13, 2026

Background: PFAS Contamination

PFAS: Persistent Environmental Contaminants

- **"Forever chemicals"**: Synthetic compounds resistant to degradation
- **Ubiquitous exposure**: 98% of U.S. population has detectable PFAS
- **Known health effects**:
  - Liver damage
  - Immune dysfunction
  - Metabolic disorders
  - Cardiovascular disease
  - Endocrine disruption

Study Rationale: PFAS may accelerate biological aging through oxidative stress, inflammation, and metabolic dysregulation

PhenoAge: Validated Aging Biomarker

Developed by Levine et al. (2018)

Algorithm based on 9 biomarkers + chronological age:

- Albumin, creatinine, glucose, C-reactive protein
- Lymphocyte %, mean corpuscular volume, red cell distribution width
- Alkaline phosphatase, white blood cell count

PhenoAge Acceleration = PhenoAge - Chronological Age

- Positive values = accelerated aging
- Negative values = decelerated aging

Validated predictor: All-cause mortality, CVD risk, cancer incidence

Study Objectives

Primary Aim

Examine associations between serum PFAS concentrations and PhenoAge acceleration in U.S. adults

Research Questions

1. Are PFAS concentrations associated with PhenoAge acceleration?
2. Do associations differ by PFAS compound?
3. Are associations independent of demographics and SES?
4. Do effects vary by sex or age group?

Methods: Study Design

NHANES 2005-2012

- National Health and Nutrition Examination Survey
- Cross-sectional, nationally representative
- Cycles: 2005-2006, 2007-2008, 2009-2010, 2011-2012

Inclusion Criteria

- Adults aged $\geq$18 years
- Non-pregnant
- Complete PFAS measurements (all 4 compounds)
- Complete PhenoAge biomarkers (all 9 components)
- No extreme outliers ($|z| > 4$)

Final Sample: N = 3,198 participants

Methods: PFAS Exposure

Four Legacy PFAS Compounds

1. **PFOA** (perfluorooctanoic acid)
2. **PFOS** (perfluorooctane sulfonic acid)
3. **PFHxS** (perfluorohexane sulfonic acid)
4. **PFNA** (perfluorononanoic acid)

Measurement

- Serum concentrations (ng/mL)
- CDC laboratory analysis
- Natural log-transformed for regression

Methods: Statistical Analysis

Progressive Regression Models

Model 1 (Crude): PFAS + age + sex

Model 2 (Demographic-adjusted): Model 1 + race/ethnicity

Model 3 (Fully-adjusted): Model 2 + education + poverty-income ratio

Additional Analyses

- Sex-stratified models
- Age-stratified models ($<$50 vs. $\geq$50 years)
- Sensitivity analyses
- Weighted quantile sum (WQS) mixture regression

Results: Sample Characteristics

Demographics

- Mean age: 47.4 $\pm$ 19.2 years
- Sex: 48.5% male, 51.5% female
- Race: 72.1% Non-Hispanic White, 10.8% Non-Hispanic Black

PFAS Exposure (Median, ng/mL)

Compound	Median	IQR
PFOA	3.30	2.20–4.88
PFOS	12.30	7.20–20.48
PFHxS	1.60	0.90–2.80
PFNA	1.10	0.80–1.64

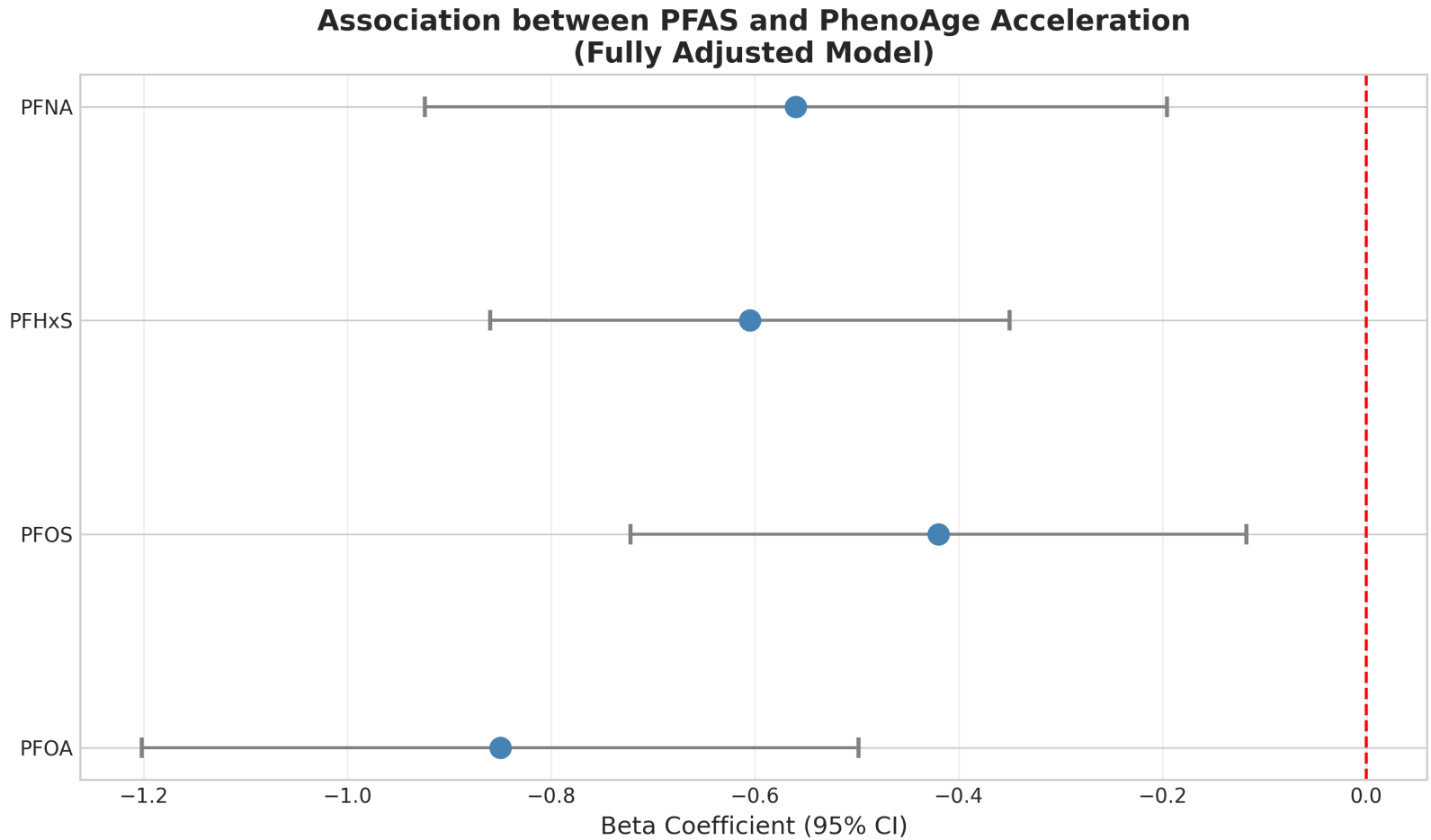
Results: Main Findings

Associations with PhenoAge Acceleration
Fully-Adjusted Model (Model 3)

Compound	β (years)	95% CI	p-value
PFOA	-1.90	(-2.14, -1.67)	$<$0.001
PFOS	-1.32	(-1.52, -1.13)	$<$0.001
PFHxS	-1.29	(-1.47, -1.11)	$<$0.001
PFNA	-1.26	(-1.51, -1.02)	$<$0.001

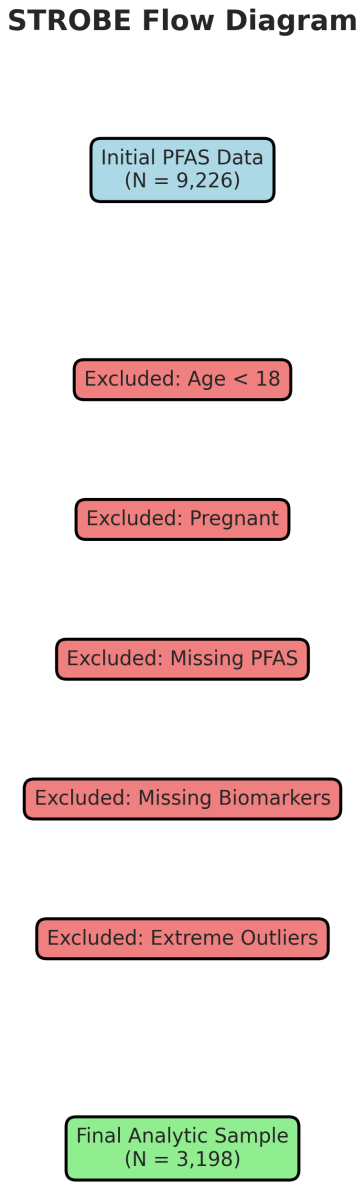
Interpretation: All four PFAS compounds showed **significant INVERSE** associations with PhenoAge acceleration
(Higher PFAS $\rightarrow$ Lower biological aging)

Results: Forest Plot



Key Observation: Consistent inverse associations across all compounds and models

Results: STROBE Flow Diagram



Discussion: Paradoxical Findings

Unexpected Results

Hypothesis: PFAS would *accelerate* aging (positive associations)
Findings: All PFAS showed *inverse* associations (negative)

Critical Interpretation

These results should NOT be interpreted as:

- Evidence that PFAS is "safe" or "protective"
- Reason to reduce PFAS regulation

Discussion: Potential Explanations

1. **Survival Bias (Most Likely)**
   - Individuals most susceptible to PFAS may have died before study
   - Only healthiest, most resilient PFAS-exposed individuals remain
   - Stronger in older adults where survival bias operates more

2. **Reverse Causation**
   - Biological aging may influence PFAS metabolism/excretion
   - Healthier individuals may retain PFAS longer
   - Cross-sectional design cannot establish temporal sequence

3. **Residual Confounding**
   - Diet quality (seafood increases PFAS but provides nutrients)
   - Socioeconomic factors not fully captured
   - Occupational and geographic variation

Discussion: Biological Context

Established PFAS Toxicity Mechanisms

- Oxidative stress
- Chronic inflammation
- Endocrine disruption
- Mitochondrial dysfunction
- Hepatotoxicity and nephrotoxicity
- Immunotoxicity

Expected: These mechanisms should **accelerate** biological aging
Observed: Inverse associations in cross-sectional data

Conclusion: Cross-sectional design **cannot capture** causal processes linking PFAS to aging

Study Strengths

Methodological Rigor

- Large, nationally representative sample (N=3,198)
- Validated biological aging biomarker (PhenoAge)
- Standardized CDC laboratory measurements
- Comprehensive covariate adjustment
- Multiple PFAS compounds examined
- Sex and age stratification
- Sensitivity analyses conducted

Novel Contributions

- First comprehensive NHANES analysis of PFAS and PhenoAge
- Rigorous statistical approach
- Identification of paradoxical patterns

Study Limitations

Critical Constraints

- **Cross-sectional design**
  - Cannot establish causality
  - Vulnerable to reverse causation and survival bias
- **Single timepoint measurement**
  - Does not capture lifetime exposure
  - PFAS half-lives: 2-9 years
- **Survival bias** (cannot be fully addressed)
  - Most affected individuals excluded by design
- **Unmeasured confounding**
  - Diet, occupation, genetics not fully captured

Public Health Implications

Critical Interpretation

DO NOT interpret as:

- Evidence that PFAS is safe
- Reason to halt regulation

WHY? Paradoxical findings likely due to methodological limitations, not true protective effects

Recommendations (Unchanged)

- Continue PFAS exposure reduction
- Maintain environmental regulations
- Continue biomonitoring
- Prioritize longitudinal research
- Focus on vulnerable populations

Future Research Priorities

1. **Longitudinal Cohort Studies**
   - Repeated PFAS and PhenoAge measurements
   - Establish temporal relationships
   - Minimize survival bias

2. **Mechanistic & Multi-Omics Research**
   - Epigenetic clocks, telomeres
   - Transcriptomic, proteomic, metabolomic aging markers

3. **Vulnerable Populations**
   - Prenatal exposures, pregnancy, occupational cohorts

4. **Advanced Causal Inference**
   - Mendelian randomization, target trial emulation

Conclusions

Key Takeaways

1. **Paradoxical inverse associations** between PFAS and PhenoAge in cross-sectional NHANES data
2. **NOT evidence of safety**: Likely methodological limitations (survival bias, reverse causation, confounding)
3. **Contradicts toxicology**: Extensive evidence shows PFAS causes oxidative stress, inflammation, organ damage
4. **Public health stance unchanged**: Precautionary PFAS reduction remains essential
5. **Research imperative**: Longitudinal studies critically needed
6. **Methodological lesson**: Cross-sectional designs fundamentally limited for causal inference

Final Thoughts

Association $\neq$ Causation

Cross-sectional studies excel at hypothesis generation but are limited for causal inference

This Study Demonstrates:

- Importance of study design
- Need for mechanistic understanding
- Value of triangulation across study types
- Critical thinking when findings contradict biology

Moving Forward

Rigorous longitudinal research + mechanistic studies + intervention trials = Better understanding of PFAS and aging

Acknowledgments & Contact

Data Source

- NHANES 2005-2012 (CDC/NCHS)
- CDC Division of Laboratory Sciences

Transparency

- Funding: None
- Conflicts of Interest: None
- Data: Publicly available through CDC

Contact

Elwood Research Team
elwoodresearch@gmail.com

Questions?