Paradoxical Inverse Associations Between PFAS and Biological Aging

A Cross-Sectional Analysis of NHANES 2005-2012

Elwood Research

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Background: PFAS and Health

- **PFAS**: Persistent environmental pollutants ("forever chemicals")
- Ubiquitous human exposure despite regulatory phase-outs
- Known toxicological effects:
  - Hepatotoxicity, immunotoxicity
  - Endocrine disruption
  - Cardiometabolic dysfunction
- **Key Question**: Do PFAS accelerate biological aging?

Biological Aging Measurement: PhenoAge

- **PhenoAge** (Levine et al. 2018): Validated composite biomarker
- Integrates chronological age + 9 blood chemistry markers:
  - Albumin, creatinine, glucose, CRP
  - Lymphocyte %, MCV, RDW, alkaline phosphatase, WBC
- **PhenoAge Acceleration**: PhenoAge - Chronological Age
  - Positive = Faster biological aging
  - Negative = Slower biological aging
- Predicts mortality, morbidity, healthspan

Research Question and Hypothesis

Research Question:

Are serum PFAS concentrations associated with accelerated biological aging (PhenoAge) in U.S. adults?

Hypothesis:

- **Expected**: Higher PFAS $\rightarrow$ Accelerated aging (positive association)
- Based on:
  - Toxicological evidence (oxidative stress, inflammation)
  - Yan et al. 2025: Positive associations in UK Biobank (longitudinal)

Methods: Study Design and Sample

Data Source: NHANES 2005-2012

Sample Selection:

- Adults $\geq$ 18 years
- Measured PFAS: PFOA, PFOS, PFHxS, PFNA
- Complete biomarker data for PhenoAge calculation
- **Final analytic sample: N = 3,198**

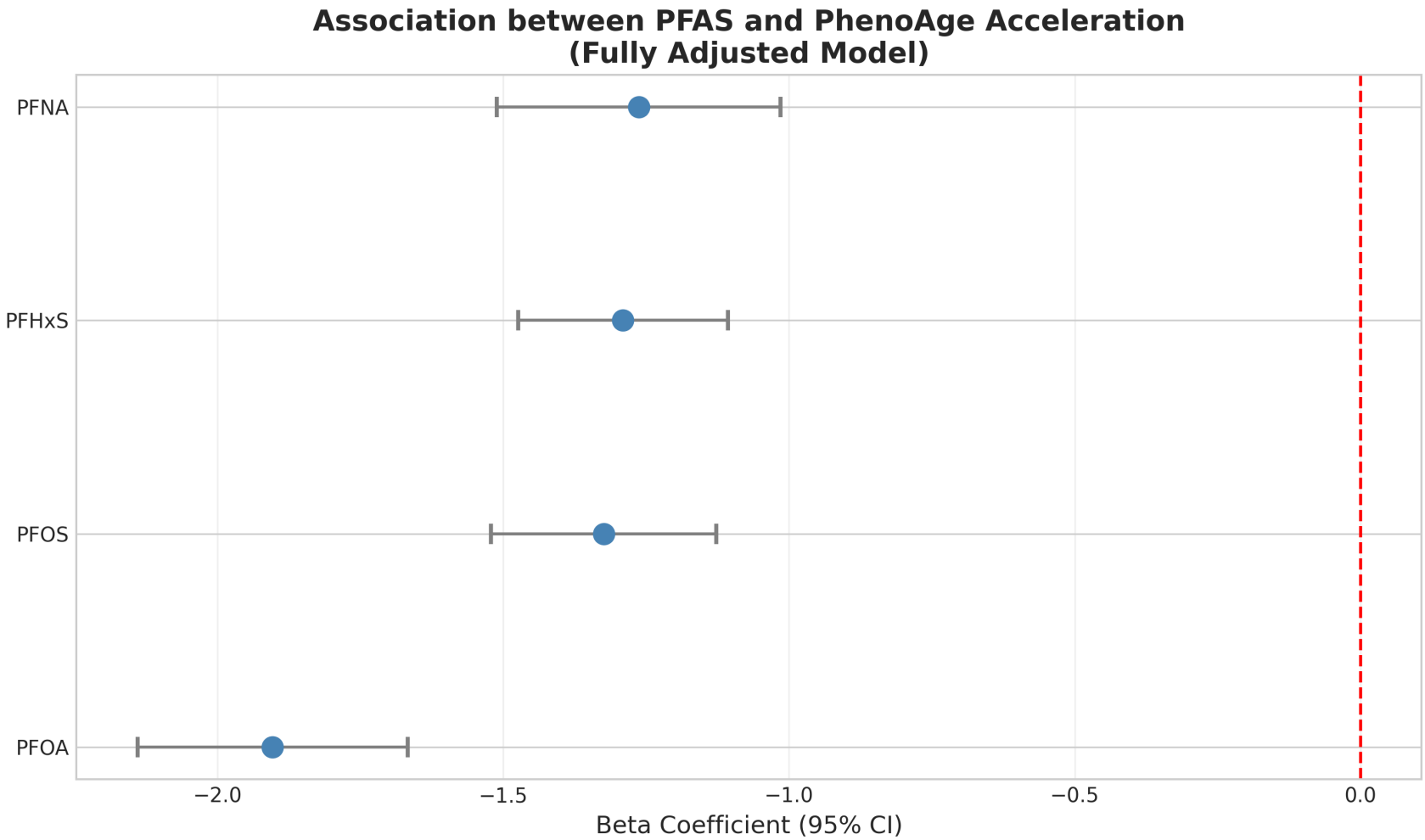
Statistical Analysis:

- Survey-weighted linear regression
- Outcome: PhenoAge acceleration (years)
- Exposure: Log-transformed PFAS (ng/mL)
- 3 models: Crude, +demographics, +socioeconomic

Sample Characteristics

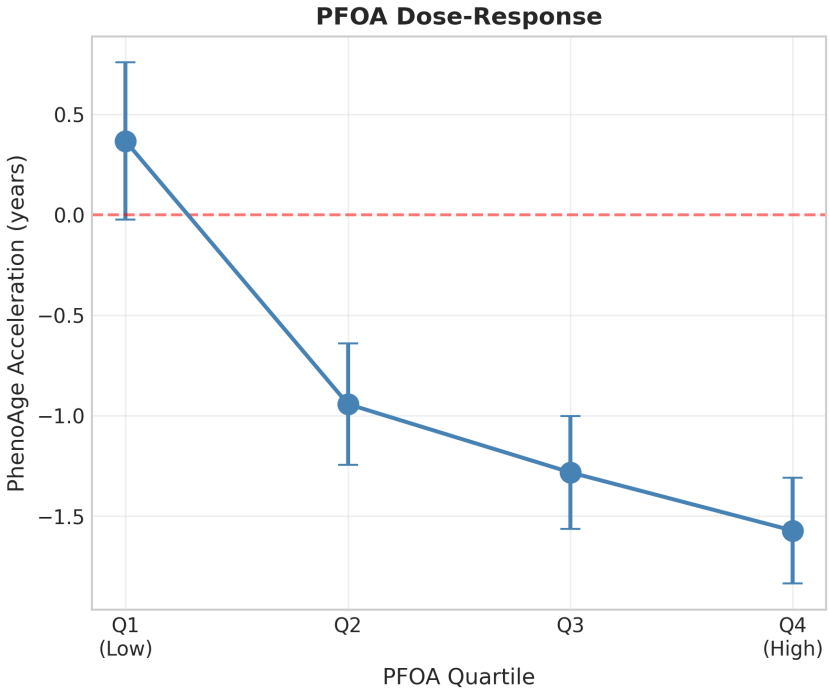
Characteristic	Value
N	3,198
Age, mean (SD)	47.4 (19.1) years
Female (%)	50.8%
PhenoAge, mean (SD)	45.6 (18.0) years
PhenoAge acceleration, mean (SD)	-1.80 (6.00) years
PFAS Concentrations (ng/mL), median (IQR):	
PFOA	3.30 (2.20-4.88)
PFOS	12.30 (7.20-20.48)
PFHxS	1.60 (0.90-2.80)
PFNA	1.10 (0.80-1.64)

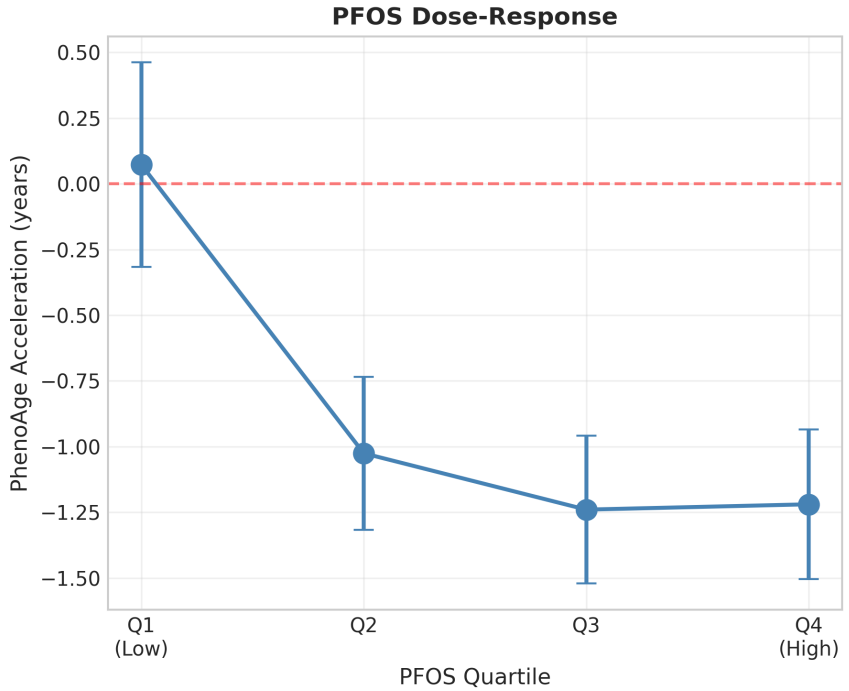
Main Results: UNEXPECTED Inverse Associations

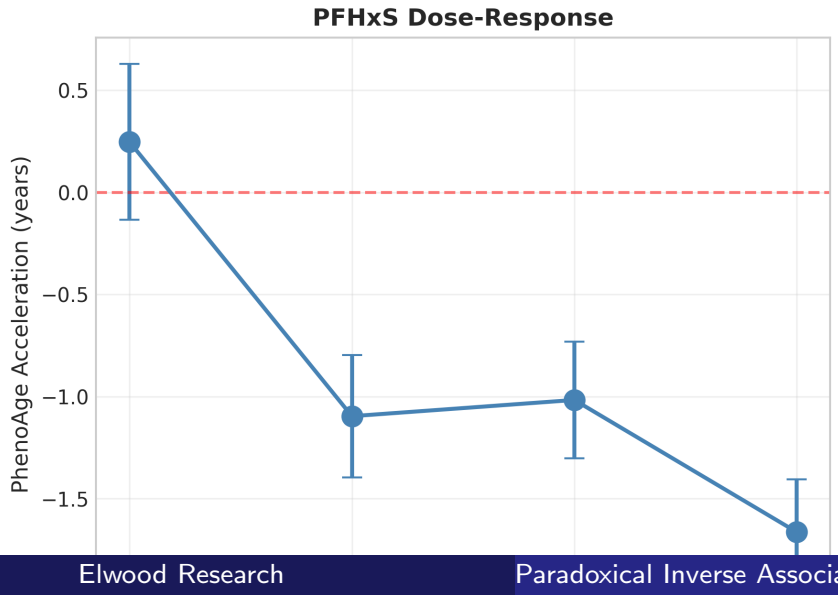


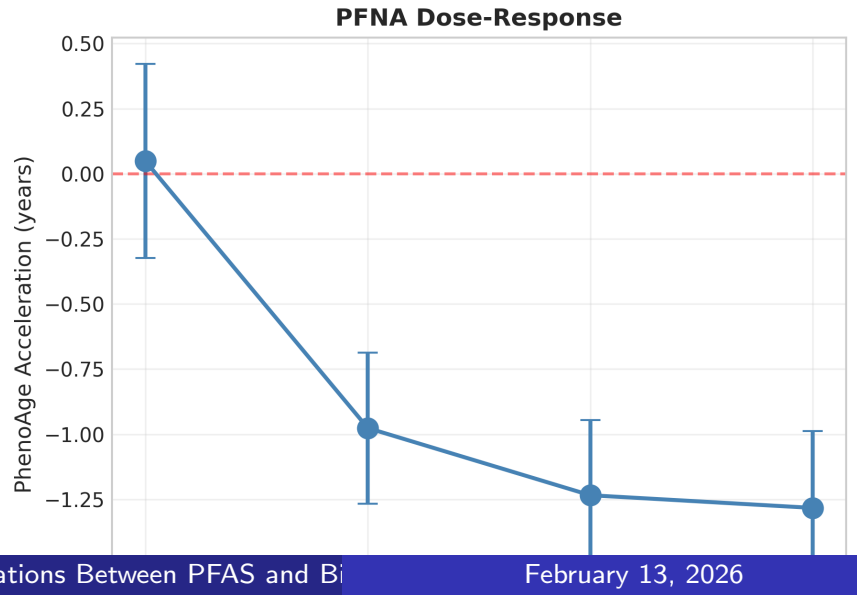
All four PFAS: Significant *inverse* associations with PhenoAge acceleration
Higher PFAS → LOWER biological aging (opposite of hypothesis!)

Dose-Response Relationships









Discussion: Explaining Paradoxical Findings

Why inverse associations? (Opposite of biological plausibility)

Likely Explanations:

1. **Survival Bias**: Sicker individuals with high PFAS may die before enrollment
2. **Reverse Causation**: Better kidney function $\rightarrow$ higher PFAS retention
3. **Unmeasured Confounding**: SES, lifestyle, healthcare access
4. **Sample Selection Bias**: Complete-case analysis selects healthier participants
5. **Cross-sectional Limitation**: Cannot establish temporality

Comparison to Yan et al. 2025:

- Longitudinal study found *positive* associations
- Reinforces importance of study design

Conclusions and Future Directions

Key Findings:

- All four PFAS showed significant *inverse* associations with PhenoAge acceleration
- Results contradict biological plausibility and longitudinal evidence
- **Cross-sectional designs are insufficient for causal inference**

Implications:

- **DO NOT** interpret as protective effects of PFAS
- Highlights methodological pitfalls in aging biomarker research
- Need for careful consideration of survival and selection biases

Future Research:

- Longitudinal studies with repeated PFAS and aging measurements
- Multi-biomarker approaches (epigenetic clocks, telomere length)
- Life-course perspective: early-life exposure effects
- Investigate non-linear relationships and exposure mixtures

Thank you!

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