5-1-2019

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The authors have no financial relationships to disclose or conflicts of interest to resolve.

Background

- Identifying factors that impair bone accrual during childhood is a critical step toward osteoporosis prevention.
- One potential risk factor not well characterized in childhood is the role of chemicals in the environment.
- Perfluoroalkyl substances (PFASs) are synthetic additives used to make clothing, furniture, and cookware stain repellant and are detectable in almost all US adults[1].
- PFASs act as PPAR-γ agonists,[2] androgen receptor antagonists,[3] and directly intercalate into bone,[4] raising the possibility that they may lead to low bone accrual.
- While two population-based studies in adults have shown associations between PFASs and low areal bone mineral density (aBMD),[5,6] the extent to which PFASs may affect aBMD in children is unknown.

Objective

Examine the associations of plasma PFAS concentrations with aBMD Z-score in mid-childhood (mean 7.9 years)

Study population (Project Viva)

Boston-area pregnant women enrolled 1999-2002 into the prospective Project Viva birth cohort

Enrolled: 2,128 mother-infant pairs → **Mid-childhood follow-up: 1,116 children** → **Plasma PFAS measured: 653 children** → **aBMD measured: 576 children**

Methods

Exposure (PFASs):

- Perfluorooctanoate (**PFOA**), perfluorooctane sulfonate (**PFOS**), perfluorodecanoate (**PFDA**), perfluorohexane sulfonate (**PFHxS**), 2-(N-methyl-perfluorooctane sulfonamido) acetate (**MeFOSAA**), perfluorononanoate (**PFNA**)
- Measured in plasma by CDC staff using on-line solid-phase extraction with isotope dilution high performance liquid chromatography mass spectrometry

Outcome (aBMD Z-score):

- Total body (excluding the skull) aBMD measured via dual-energy X-ray absorptiometry (DXA)
- Analyzed DXA data with pediatric software (Hologic, version 12.6) and used U.S. national reference data to derive age-, sex-, race-, and height-adjusted aBMD Z-scores.[7]

Statistical analyses:

- Used linear regression to examine associations of each PFAS with aBMD Z-score separately in single-PFAS models, and mutually adjusted with other PFASs in a multi-PFAS model
- Examined association between the PFAS mixture and aBMD Z-score via weighted quantile sum (WQS) regression. WQS generates a composite mixture index for each participant, assigning each PFAS within the mixture a weight reflecting:
  - ➢ Strength of its association with aBMD Z-score
  - ➢ Collinearity with other PFASs within mixture
- Log_2 transformed plasma PFAS concentrations for linear associations with outcome
- Covariates in final models were maternal age, education, annual household income, census tract median household income, and child age, sex, race/ethnicity, and dairy intake, physical activity, and year of blood draw
- No evidence for effect modification by sex, so present results without an interaction term

Results

Table 1. Participant characteristics overall and by PFOA plasma concentration

		Quartiles of PFOA [a] plasma concentration			
	Overall n=576	Q1 n=145	Q2 n=147	Q3 n=140	Q4 n=144
	Mean ± SD or n (%)				
Maternal characteristics					
Maternal age at enrollment (years)	31.8 ± 5.7	29.8 ± 6.5	31.6 ± 5.9	32.7 ± 5.0	33.1 ± 4.5
College graduate (%)	364 (64)	59 (41)	89 (61)	101 (73)	115 (80)
Individual household income (%)					
< $40,000/year	85 (16)	39 (30)	20 (14)	15 (11)	11 (8)
$40,001-$70,000/year	89 (16)	25 (19)	23 (17)	22 (16)	19 (13)
> $70,000/year	369 (68)	65 (51)	96 (69)	98 (73)	110 (79)
Census tract median household income ($10,000/year)	62.7 ± 23.7	53.5 ± 21.0	60.4 ± 23.2	64.7 ± 21.0	72.4 ± 25.5
Child characteristics					
Age (years)	7.9 ± 0.8	8.2 ± 1.0	8.0 ± 0.8	7.8 ± 0.7	7.7 ± 0.6
Female (%)	280 (49)	73 (50)	73 (50	101 (45)	71 (49)
Race/ethnicity (%)					
White	328 (57)	37 (26)	80 (54)	94 (68)	117 (81)
Black	129 (23)	66 (46)	32 (22)	21 (15)	10 (7)
Other	117 (20)	41 (28)	35 (24)	24 (17)	17 (12)
Dairy intake (servings/wk)	2.2 ± 1.5	2.0 ± 1.5	2.2 ± 1.5	2.3 ± 1.6	2.4 ± 1.5
Physical activity (hrs/wk)	1.9 ± 1.4	1.9 ± 1.5	1.7 ± 1.3	1.9 ± 1.2	1.9 ± 1.5
aBMD Z-score	-0.86 ± 0.77	-0.73 ± 0.73	-0.81 ± 0.84	-0.95 ± 0.73	-0.93 ± 0.78

[a] PFOA quartile minimum and maximum values: <0.1 (LOD)-3.0 ng/mL for Q1, 3.1-4.4 ng/mL for Q2, 4.5-6.1 ng/mL for Q3, and 6.2-14.3 ng/mL for Q4

Table 2. Plasma PFAS concentration distributions and correlations

	Plasma PFAS concentrations (ng/mL)					
	PFOA	PFOS	PFDA	PFHxS	MeFOSAA	PFNA
Median (IQR)	4.4 (3.2)	6.4 (5.6)	0.3 (0.3)	1.9 (2.3)	0.3 (0.5)	1.5 (1.2)
5th percentile	1.9	2.1	< LOD [a]	0.6	< LOD [a]	0.7
95th percentile	9.8	18.7	0.7	14.7	1.9	5.1
Detection frequency (%)	99.5	99.5	88.4	99.5	65.6	99.5
	Spearman correlation coefficients					
PFOA	1.00					
PFOS	0.79	1.00				
PFDA	0.69	0.59	1.00			
PFHxS	0.60	0.67	0.34	1.00		
MeFOSAA	0.50	0.63	0.32	0.37	1.00	
PFNA	0.43	0.35	0.57	0.13	0.22	1.00

[a] Limit of detection (LOD) was 0.1 ng/mL for all PFASs

Figure 1. Single and multi-PFAS models showing adjusted associations of individual PFAS plasma concentrations with aBMD Z-score

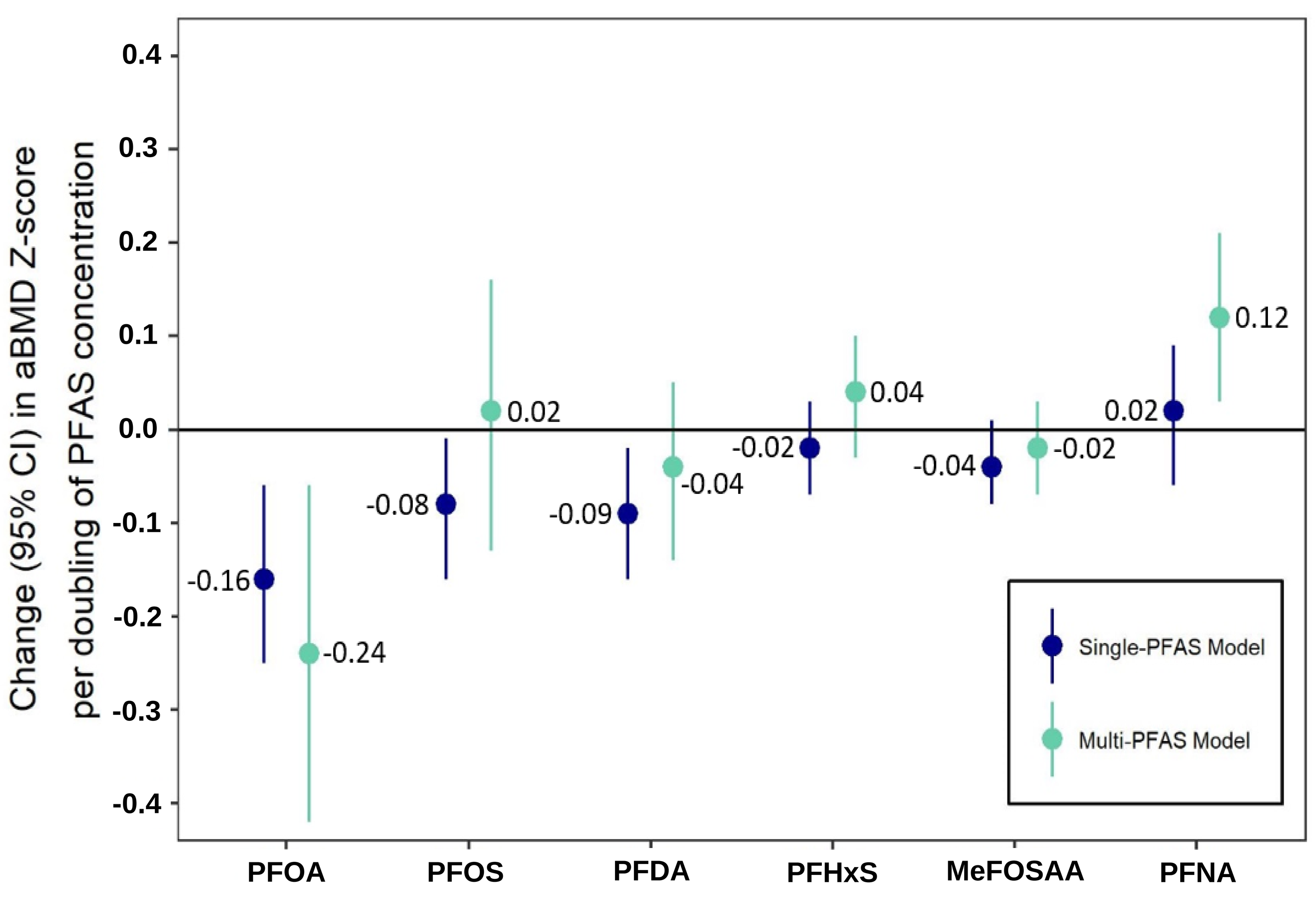
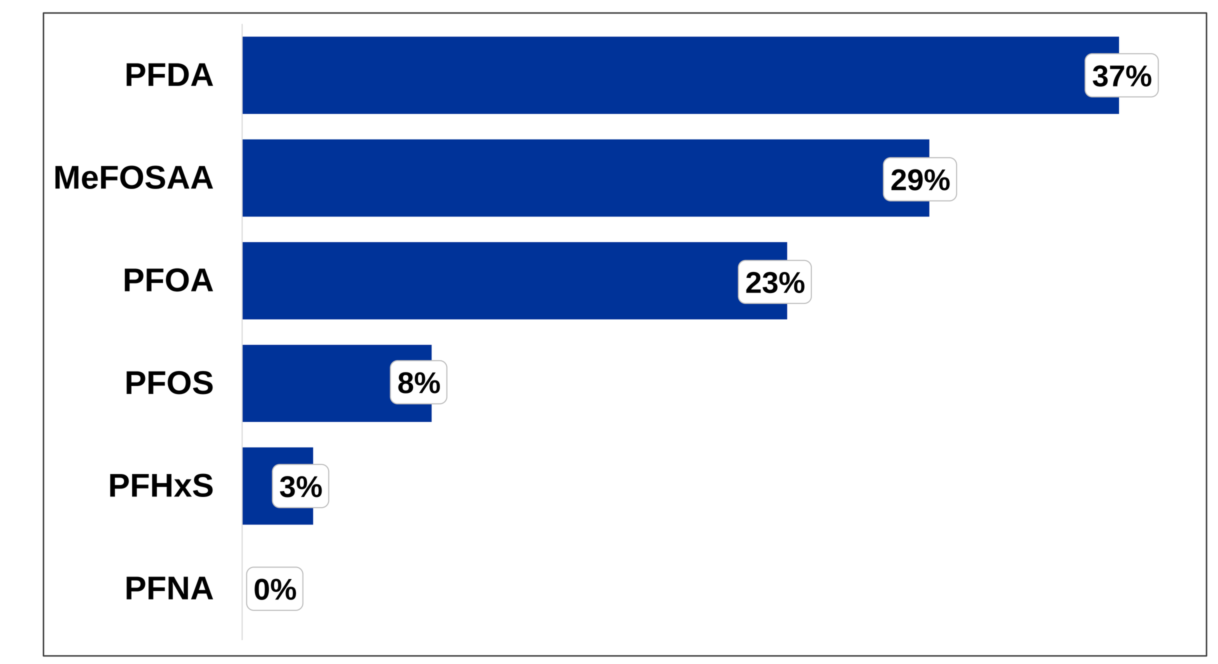


Figure 2. Weights assigned to individual PFASs within the WQS composite index



Each IQR increment in the WQS index was associated with a -0.16 lower aBMD Z-score (95% CI: -0.28, -0.04).

Strengths and Limitations

Strengths

- Among the first studies to evaluate role of toxicants on bone health in childhood
- PFAS concentrations typical for US population during peak production
- Used WQS regression to assess exposure to PFAS mixture

Limitations

- High SES cohort limits generalizability
- Cross sectional analysis, so unable to assess mediation by BMI or pubertal status

Conclusions

- Higher exposure to PFASs was associated with lower aBMD Z-scores in children.
- Lower exposures to environmental toxicants such as PFASs may improve childhood bone accrual and optimize lifelong skeletal health.

Acknowledgements

We thank the staff and participants of Project Viva for their support. We also thank CDC staff for conducting PFAS measurements.

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The authors have received support from the National Institutes of Health (NIEHS R01ES021447, NICHD R01HD034568, NIEHS K23ES024803, OD UG3OD023286, NIEHS R01ES030101)