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# Per- and Polyfluoroalkyl Substances and Bone Mineral Density in Mid-childhood



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## Background

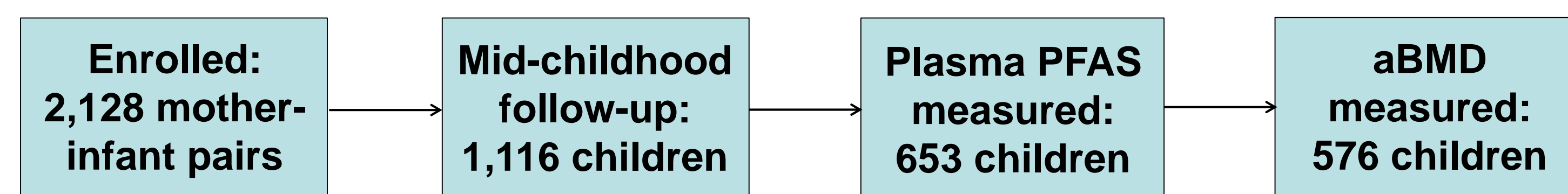
- Identifying factors that impair bone accrual during childhood is a critical step toward osteoporosis prevention.
- One potential risk factor not well characterized in childhood is the role of chemicals in the environment.
- Perfluoroalkyl substances (PFASs) are synthetic additives used to make clothing, furniture, and cookware stain repellent and are detectable in almost all US adults<sup>1</sup>.
- PFASs act as PPAR- $\gamma$  agonists,<sup>2</sup> androgen receptor antagonists,<sup>3</sup> and directly intercalate into bone,<sup>4</sup> 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),<sup>5,6</sup> 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



## 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.<sup>7</sup>

### 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<sub>2</sub> 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

|  | Overall<br>n=576 | Quartiles of PFOA <sup>a</sup> plasma concentration |                  |                  |                  |
|--|------------------|---|------------------|------------------|------------------|
|  |                  | Q1<br>n=145   | Q2<br>n=147      | Q3<br>n=140      | Q4<br>n=144      |
|  |                  | Mean $\pm$ SD or n (%)                              |                  |                  |                  |
| <b>Maternal characteristics</b>                      |                  |   |                  |                  |                  |
| Maternal age at enrollment (years)                   | 31.8 $\pm$ 5.7   | 29.8 $\pm$ 6.5                                      | 31.6 $\pm$ 5.9   | 32.7 $\pm$ 5.0   | 33.1 $\pm$ 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 $\pm$ 23.7  | 53.5 $\pm$ 21.0                                     | 60.4 $\pm$ 23.2  | 64.7 $\pm$ 21.0  | 72.4 $\pm$ 25.5  |
| <b>Child characteristics</b>                         |                  |   |                  |                  |                  |
| Age (years)  | 7.9 $\pm$ 0.8    | 8.2 $\pm$ 1.0                                       | 8.0 $\pm$ 0.8    | 7.8 $\pm$ 0.7    | 7.7 $\pm$ 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 $\pm$ 1.5    | 2.0 $\pm$ 1.5                                       | 2.2 $\pm$ 1.5    | 2.3 $\pm$ 1.6    | 2.4 $\pm$ 1.5    |
| Physical activity (hrs/wk)                           | 1.9 $\pm$ 1.4    | 1.9 $\pm$ 1.5                                       | 1.7 $\pm$ 1.3    | 1.9 $\pm$ 1.2    | 1.9 $\pm$ 1.5    |
| aBMD Z-score   | -0.86 $\pm$ 0.77 | -0.73 $\pm$ 0.73                                    | -0.81 $\pm$ 0.84 | -0.95 $\pm$ 0.73 | -0.93 $\pm$ 0.78 |

<sup>a</sup> 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) |
| 5 <sup>th</sup> percentile  | 1.9                                | 2.1       | < LOD <sup>a</sup> | 0.6       | < LOD <sup>a</sup> | 0.7       |
| 95 <sup>th</sup> 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      |

<sup>a</sup> Limit of detection (LOD) was 0.1 ng/mL for all PFASs

## 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.

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

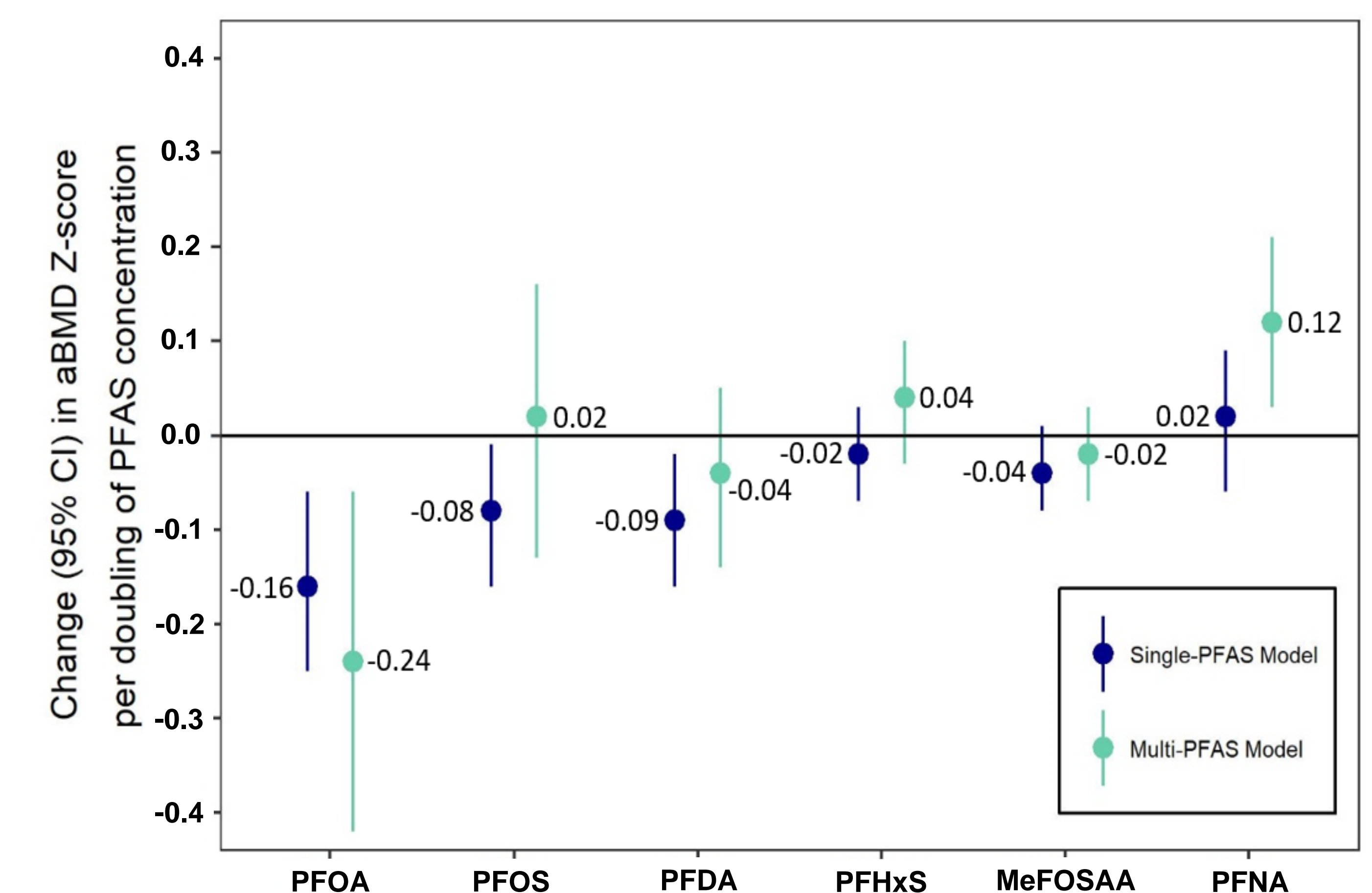
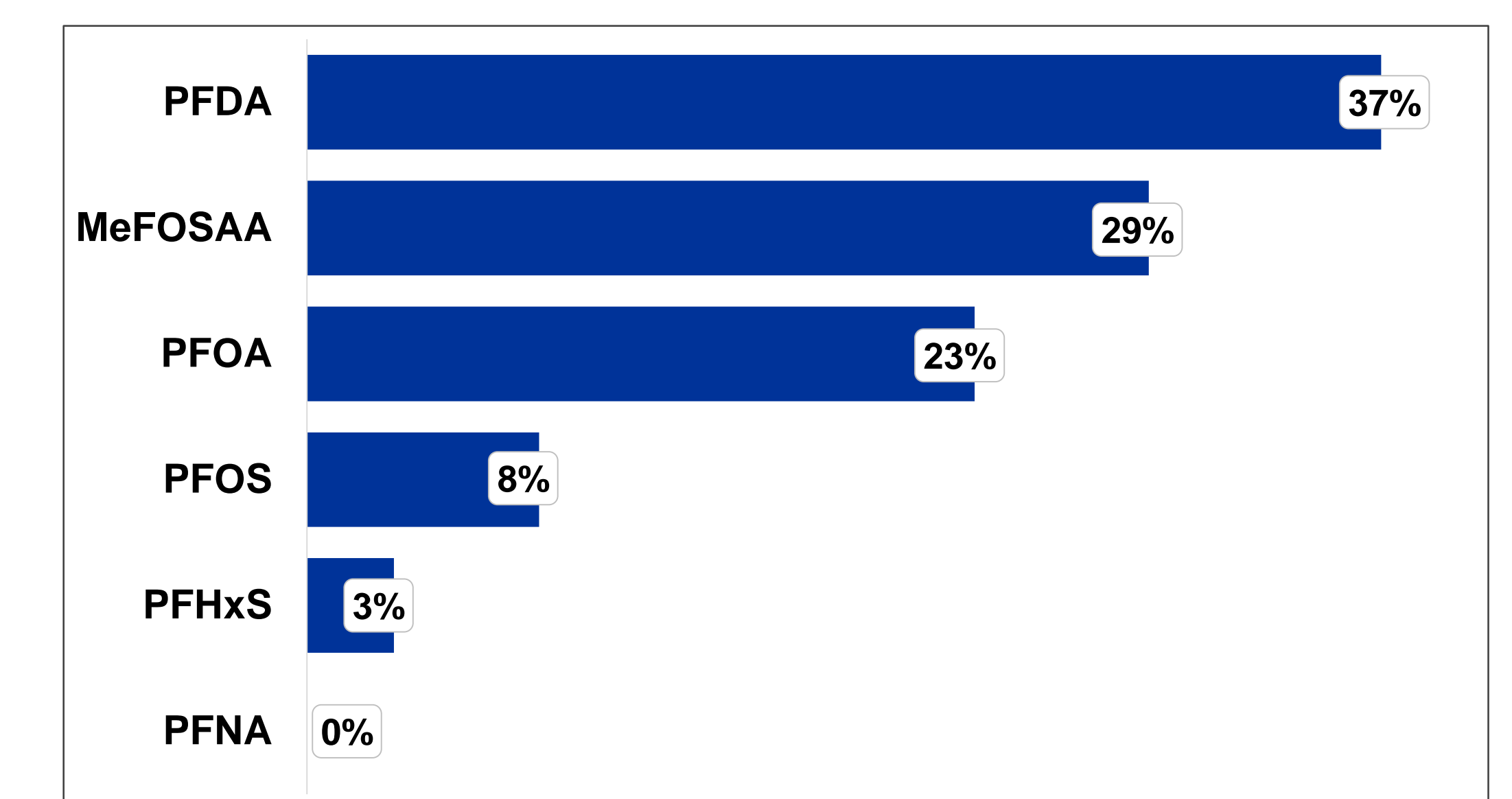


Figure 2. Weights assigned to individual PFASs within the WQS composite index



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