Occupational Diseases and Environmental Medicine, 2021, 9, 93-111
https://www.scirp.org/journal/odem
ISSN Online: 2333-357X
ISSN Print: 2333-3561

Analysis of PFAS Levels and Associations with Adolescent Anthropometric Outcomes in NHANES

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How to cite this paper: Sutherland, D., Le Beau, A., Bourgeois, M. and Harbison, R. (2021) Analysis of PFAS Levels and Associations with Adolescent Anthropometric Outcomes in NHANES. *Occupational Diseases and Environmental Medicine*, **9**, 93-111.
https://doi.org/10.4236/odem.2021.93008

Received: May 14, 2021
Accepted: June 15, 2021
Published: June 18, 2021

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Abstract

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are found in some consumer products due to their heat resistance and durability. However, there is potential for these substances to bioaccumulate in humans. It is relevant to investigate biological effects of these chemicals, as studies have suggested early life exposure may impact human developmental outcomes such as infant birth weight and youth adiposity. The objective of the current study was to determine if a relationship exists between increasing levels of certain PFAS and anthropometrics in adolescents ages 12 - 18. The three PFAS examined were: perfluorodecanoic acid (PFDeA), 2-(N-methyl-perfluoroctane sulfonamido) acetic acid (Me-PFOSA-AcOH), and perfluoroundecanoic acid (PFUA). The data was obtained from the National Health and Nutrition Examination Survey (NHANES) from the years 2011-2012 (N = 287) and 2013-2014 (N = 344). An additional analysis combined data from 3 NHANES survey cycles using sampling weights for the years 2011-2016 (N = 875) to generate a larger sample size of detectable PFAS. PFAS concentrations were classified as above or below the lower limit of detection (LLOD) to evaluate differences in weight, waist circumference, BMI (body mass index), and height using Student's t-tests. These same anthropometric outcomes were examined as continuous variables in linear regression models and were stratified by sex. In the 2013-2014 dataset, there were significant inverse associations between female concentrations of PFUA and PFDeA with waist circumference (PFUA β = −0.056; 95% CI, −0.106, −0.005; PFDeA β = −0.06; 95% CI, −0.10, −0.02), weight-for-age z-score (PFUA β = −0.40; 95% CI, −0.74, −0.05; PFDeA β = −0.38; 95% CI, −0.64, −0.12), and BMI-for-age z-score (PFUA β = −0.48; 95% CI, −0.86, −0.10; PFDeA β = −0.45; 95% CI, −0.73, −0.16). In the 2011-2012 dataset, males displayed a significant inverse

relationship between PFDeA and waist circumference (β = −0.08; 95% CI, −0.14, −0.02), weight-for-age z-score (β = −0.49; 95% CI, −0.88, −0.11), and BMI-for-age z-score (β = −0.44; 95% CI, −0.84, −0.05). In the combined analysis of NHANES years 2011-2016, there were significant inverse associations with PFUA and PFDeA and weight-for-age z-score, waist circumference, and BMI-for-age z-score. In the given sample years, there was no compelling evidence for a relationship between any of the perfluoroalkyl chemicals and height, nor between Me-PFOSA-AcOH and any of the body measures after adjusting for age, sex, and race/ethnicity. This suggests that PFUA and PFDeA exposure in adolescents may be related to smaller waist circumference, weight, and BMI, but longitudinal studies are recommended to confirm these findings.

Keywords

Perfluoroalkyl Substances, PFAS, BMI, Height, NHANES

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are manufactured for use in makeup, food packaging, nonstick pots and pans, stain and water-resistant coatings, firefighting foams, and paints [1] [2] [3]. The principal exposure routes include the ingestion of contaminated drinking water and food; other methods of exposure include household dust inhalation or ingestion, as well as some dermal absorption through products containing PFAS [2] [4] [5]. Elimination of PFAS from the body occurs mainly through urine, although excretions via feces, breastmilk, and menstruation have been shown to take place as well [5]. The half-lives for PFAS may be drastically different depending upon the specific subtype, with longer chain PFAS requiring more time for elimination [5] [6]. For example, the half-life for both PFDeA (perfluorodecanoic acid) and PFUA (perfluoroundecanoic acid) in humans aged 50 years and younger is 12 years on average; this is substantially longer than the half-life elimination for most other perfluoroalkyl chemicals which may be due in part to their long carbon chains [5] [6]. Longer chain PFAS have enhanced affinity for binding albumin in serum and the liver as well as a reduced elimination rate from the body, thereby allowing them to bioaccumulate [5] [7].

Historically, PFAS have been created through the process of electrochemical fluorination (ECF) by which hydrogen atoms are exchanged for fluorine atoms to yield linear structures and branched isomers [5] [7] [8]. This process is utilized less frequently today, as it has been replaced with telomerization to produce mainly linear PFAS [5]. The strength of the carbon-fluorine bond as well as the hydrophobic and lipophobic qualities of these substances makes them ideal for use as surfactants in water and oil-resistant products [1] [8] [9]. These properties confer resistance to degradation, thereby permitting PFAS to remain in

measurable quantities in human and animal sera as well as in the environment [8] [10]. The observed environmental persistence of perfluoroalkyl substances and their widespread detection rates in human biological samples have prompted researchers to investigate the possible impacts of exposure.

There have been mixed findings regarding the associations between PFAS levels in biological samples and child developmental outcomes. Current literature reports disparate effects of PFAS exposure on body weight, with many of these differences being age-dependent. A lack of association between infant birthweight and maternal PFOS (perfluorooctane sulfonic acid), PFOA (perfluorooctanoic acid), and PFHxS (perfluorohexane sulfonic acid) concentrations have been noted in multiple studies [11] [12] [13] [14]. However, other investigators have reported significantly reduced birthweights observed alongside increasing maternal levels of PFNA (perfluorononanoic acid), PFUA, PFDeA, or PFOS [15] [16] [17] [18] [19]. Even so, there is doubt as to whether any observed effects with birthweight persist into early childhood and adulthood. Two longitudinal studies which examined *in utero* PFOA exposure found that it was significantly related to reduced birthweight; however, the association with weight diminished to become nonsignificant at 5 months [20] and 20 months [21].

Other studies have found associations between PFAS and weight outcomes in the opposite direction, reporting increased adiposity in children and adults. Studies examining PFOA in cord blood or maternal serum have found significant associations with increased body fat in 8-year-olds [22] and significantly higher risk for overweight in children at 5 years of age, but not at 18 months [23]. Gestational PFOS and PFOA concentrations in a non-primiparous mother and child paired cohort have been related to significantly increased BMI-for-age-and-sex z-score as well as greater triceps skinfold z-score in Norwegian children at 5 years, but neither measure was significant in the Swedish group of children [24]. A longitudinal study from Denmark found that prenatal exposure to PFOA was significantly associated with greater weight in female adult offspring at 20 years of follow-up, but not with PFNA or PFOS after controlling for PFOA concentrations [25]. A meta-analysis of the aforementioned prospective studies noted a significant pooled effect estimate between prenatal PFOA exposure and relative risk for overweight; however, the pooled odds ratio narrowly missed the significance level [26]. A cross-sectional NHANES analysis has noted increased odds of obesity in 12 - 18-year-old adolescents with higher PFOA exposure, but not with PFOS [27]. Conversely, a separate cross-sectional analysis of children ages 8 - 10 found that associations between PFOA and PFOS with BMI, skinfold thickness, waist circumference, adiponectin, and leptin were null; however, greater insulin resistance in overweight children correlated with PFOA and PFOS in child serum [28].

Another area that has been investigated for its possible relationship with PFAS exposure is height outcomes, where the associations have generally been inverse, but not all findings have been significant. In children at 2 years of age, higher

serum levels of PFHxS, PFOS, PFOA, PFNA, and PFDeA were associated with decreased height outcomes, but only PFHxS, PFOA, and PFOS were significantly associated with the change in height from birth to 2 years of age follow up [29]. PFUA, and particularly PFDeA, were associated with shorter average height z-scores in female children who were measured repeatedly from age 2 to 11; however, many of the heights were not consistently significant when looking at each age year individually, and none of the average height z-scores were significant in males [30]. An NHANES study looking at weight in children ages 3 - 11 found no significant relationship between PFOS, PFOA, and PFNA with height-for-age z-score (HAZ), although boys displayed significantly reduced HAZ in association with higher PFHxS [31]. In infants, it was noted that maternal exposure to PFOS, PFNA, PFDeA, PFUA and PFDoA during the first trimester was inversely associated with length of newborn female infants, but mothers' plasma collected later during gestation or post-delivery showed no significant relationships with birthweight, length, and head circumference [18]. Nonsignificant associations between maternal cord serum concentrations of PFUA, PFDeA, PFHxS, PFOS, PFOA, and PFNA with birth length have also been reported in both crude models and models adjusted for maternal age and parity [32].

PFAS have been implicated as possible endocrine disruptors, displaying xenoestrogenic activity [33] and possibly affecting pubertal development in girls [34]. Thus, it is pertinent to investigate the potential effects of PFAS exposure on body maturation during the adolescent years. In this analysis, three PFAS were examined including perfluorodecanoic acid (PFDeA), 2-(N-methyl-perfluoroctane sulfonamido) acetic acid (Me-PFOSA-AcOH), and perfluoroundecanoic acid (PFUA). The objective was to determine if a relationship exists between concentrations of these PFAS and anthropometric outcomes in adolescents ages 12 - 18 using a sample of NHANES data.

2. Methods

2.1. Sample

The data was obtained from 2 survey cycles of the National Health and Nutrition Examination Survey (NHANES) from the years 2011-2012 and 2013-2014 (additional analysis includes combined years 2011-2016; refer to supplement). NHANES is a nationally representative survey that is conducted by the Centers for Disease Control and Prevention (CDC) for the National Center of Health Statistics (NCHS) to monitor the health of U.S. residents. Individuals are excluded if they live in institutionalized group settings such as prisons or care facilities, or if they are active military personnel and their relatives living on a military base, or anyone residing outside of the 50 U.S. states and District of Columbia [35]. NHANES uses a four-stage probability sampling procedure from which participants are drawn to respond to questionnaires, receive physical examinations, and provide laboratory specimens [36]. The available subject data from each dataset was matched on PFAS, anthropometrics, age, gender, and

ethnicity variables by the identifying participant sequence number. A total of 287 participants from 2011-2012 NHANES and 344 participants from 2013-2014 NHANES with complete information on PFAS exposure and relevant covariates were included in the primary analysis after those with missing data were excluded.

2.2. Perfluoroalkyl Substances Detection

The effects of exposure to three PFAS were considered: perfluorodecanoic acid (PFDeA), 2-(N-methyl-perfluoroctane sulfonamido) acetic acid (Me-PFOSA-AcOH), and perfluoroundecanoic acid (PFUA). The PFAS used in this analysis were chosen for ease of comparison of average anthropometric values between those above and below the lower limit of detection (LLOD). Only participants aged 12 years and over were eligible to have their serum tested for the presence of perfluoroalkyl chemicals. The serum levels of perfluoroalkyl substances were collected in a one-third subsample of NHANES participants using High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry with online-solid phase extraction. The LLOD of each PFAS was 0.10 ng/mL, except in the 2011-2012 survey cycles which used 0.09 ng/mL as the LLOD for Me-PFOSA-AcOH. Values below the lower limit of detection were imputed by dividing the LLOD by the square root of two (LLOD/$\sqrt{2}$). Thus, the imputed PFAS concentrations were reported as 0.07 ng/mL (or as 0.06 ng/mL for Me-PFOSA-AcOH in 2011-2012 NHANES) [37].

2.3. Statistical Procedures

Detection status was dichotomized as above or below the detection limit for each PFAS. Unweighted, independent samples *t*-tests were used to assess differences in mean waist circumference, BMI, weight, and height between those with detectable and undetectable levels of PFUA, PFDeA, and Me-PFOSA-AcOH in years 2011-2012 and 2013-2014, separately. Normality of data was assessed using the Shapiro-Wilk test. Weight (kg), waist circumference (cm), BMI (body mass index) (kg/m^2), and height (m) were natural log-transformed to achieve a normalized distribution using the geometric mean which is less sensitive to extreme values. Thus, geometric means are given for these continuous outcomes. Where homogeneity of variances could be assumed, pooled *p*-values were utilized; otherwise, the Satterthwaite approximation was used. Additionally, the analysis was stratified by sex to isolate the effect of gender.

Unweighted, multiple linear regression was performed to evaluate associations between the three PFAS (PFUA, PFDeA, and Me-PFOSA-AcOH) and each anthropometric outcome (weight, waist circumference, BMI, and height), holding all other predictors constant. The concentrations of PFUA, PFDeA, and Me-PFOSA-AcOH were natural log-transformed to compensate for the skew created by the large number of non-detects in the data. All outcomes except for log-transformed waist circumference were standardized as BMI-for-age (BMIZ), weight-for-age (WAZ), and height-for-age z-scores (HAZ) according to the SAS

program for CDC growth chart [38]. All models were checked for constant variance and outliers. The CDC program automatically flags extreme BMIZ, WAZ, and HAZ values deemed "biologically implausible," but no such values were found in these data.

Regression models were controlled for age (12 - 18 years), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other). Models depicting weight-related outcomes specifically adjusted for height, and models where height was the dependent variable were adjusted for weight. Stratification by sex tested for differences in BMI-for-age z-score, weight-for-age z-score, height-for-age z-score, and waist circumference in males and females. Parameter estimates including beta coefficients and their 95% confidence intervals were generated. Significance was set at $p < 0.05$.

Due to the low count of participants with detectable levels of these selected PFAS, an additional analysis was conducted on the combination of data from three survey cycles of NHANES: years 2011-2012, 2013-2014, and 2015-2016. Independent samples *t*-tests were performed, and regression models were fit on the combined sample of individuals using the sample weights provided by NHANES ($N = 875$). The sample weights, strata, and clusters were incorporated into the variance estimates using the Taylor Series Linearization method through PROC SURVEYREG and PROC SURVEYMEANS procedures according to the methods prescribed by the Centers for Disease Control and Prevention (CDC). Subsample weights for those with serum tested for PFAS were determined by the inverse probability of selection divided by three to represent NHANES data from three survey years combined [39]. Controlling for the clustered design accounts for the correlations between subject data derived from the same counties, city blocks, or households. The sample weights correct for the oversampling of minority groups in NHANES data, unequal probability of selection, and nonresponse. Although aggregating multiple survey years increases statistical power, this is tempered by larger variance estimates that are generated when accounting for weighting, stratification, and clustering. Thus, these methods for combing survey years are regarded as more conservative (see supplement).

For the Student's *t*-tests on 2011-2016 combined survey years, only waist circumference and BMI were natural log-transformed, and therefore their geometric means were reported. Weight and height conformed to a normal distribution without transformation, and their arithmetic means were utilized in the *t*-tests. Regression models on the combined NHANES years controlled for age (12 - 18 years), sex, race/ethnicity (non-Hispanic white (reference), non-Hispanic black, Hispanic, other), annual family income in dollars, height (m), weight (kg), number of hours of TV and videos watched per day in the past 30 days, vigorous work or exercise in a typical week (yes/no), and number of meals not prepared at home in the past 7 days (*i.e.* food obtained from restaurants, fast food places, food stands, grocery stores, or from vending machines). The selected covariates were *a priori* risk factors for youth body development and their inclusion was based on results generated from stepwise selection methods and lower Akaike's

information criterion (AIC) while still including the PFAS of interest. No multicollinearity was present according to variance inflation and tolerance estimates. Models were fit regressing BMI-for-age z-score, weight-for-age z-score, height-for-age z-score, and waist circumference on each natural log-transformed PFAS. A differential effect of gender was tested by stratifying on participant sex, and by adding an interaction term between each continuous PFAS variable and sex within the multivariate regression. All parts of the analysis were conducted using SAS version 9.4 (SAS Institute, Inc. Cary, NC).

3. Results

3.1. Descriptive Statistics

In the sample from 2011-2012 NHANES (N = 287), males represented 50.52% (n = 145) and females 49.48% (n = 142). In 2013-2014 NHANES (N = 344), males comprised 53.78% (n = 185) and females 46.22% (n = 159). The average age of males and females in each NHANES survey year was approximately 15 years (Table 1). The geometric means and standard deviations of the PFAS in the

Table 1. Characteristics of 2011-2012 and 2013-2014 NHANES participants aged 12 - 18 years who were tested for perfluoroalkyl substances.

Characteristic	2011-2012 NHANES			2013-2014 NHANES		
	Both sexes	Males	Females	Both sexes	Males	Females
N	287	145	142	344	185	159
Age, M (SD)	14.87 (1.94)	14.86 (1.94)	14.88 (1.94)	15.08 (1.96)	15.19 (1.97)	14.96 (1.95)
Race/ethnicity, *n* (%)						
Non-Hispanic white	64 (22.30%)	33 (22.76%)	31 (21.83%)	93 (27.03%)	54 (29.19%)	39 (24.53%)
Non-Hispanic black	86 (29.97%)	48 (33.10%)	38 (26.76%)	79 (22.97%)	45 (24.32%)	34 (21.38%)
Hispanic	81 (28.22%)	40 (27.59%)	41 (28.88%)	123 (35.76%)	63 (34.05%)	60 (37.73%)
Other	56 (19.51%)	24 (16.55%)	32 (22.54%)	49 (14.24%)	23 (12.43%)	26 (16.35%)
PFUA (ng/mL), GM (SD)	0.10 (1.77)	0.10 (1.77)	0.10 (1.77)	0.09 (1.62)	0.09 (1.64)	0.09 (1.61)
Min-max (ng/mL)	0.07 - 0.58	0.07 - 0.58	0.07 - 0.56	0.07 - 0.80	0.07 - 0.80	0.07 - 0.70
Detection rate (%)	41.11%	38.62%	43.66%	20.93%	22.16%	19.50%
PFDeA (ng/mL), GM (SD)	0.15 (1.74)	0.15 (1.72)	0.14 (1.75)	0.13 (1.88)	0.14 (1.94)	0.13 (1.81)
Min-max (ng/mL)	0.07 - 0.64	0.07 - 0.63	0.07 - 0.64	0.07 - 1.70	0.07 - 1.70	0.07 - 1.30
Detection rate (%)	77.00%	80.69%	73.24%	69.48%	71.35%	67.30%
Me-PFOSA-AcOH (ng/mL), GM (SD)	0.12 (2.38)	0.14 (2.52)	0.11 (2.21)	0.11 (2.10)	0.12 (2.10)	0.11 (2.09)
Min-max (ng/mL)	0.06 - 3.29	0.06 - 3.29	0.06 - 1.24	0.07 - 2.00	0.07 - 1.80	0.07 - 2.00
Detection rate (%)	54.01%	57.93%	50.00%	43.02%	47.03%	38.36%
Weight (kg), GM (SD)	64.01 (1.34)	68.45 (1.35)	59.77 (1.32)	64.44 (1.32)	68.73 (1.33)	59.78 (1.28)
Waist circumference (cm), GM (SD)	80.97 (1.21)	82.15 (1.21)	79.79 (1.20)	81.34 (1.19)	82.96 (1.20)	79.49 (1.17)
BMI (kg/m^2), GM (SD)	23.71 (1.29)	23.88 (1.29)	23.54 (1.28)	23.69 (1.26)	23.93 (1.27)	23.40 (1.25)
Height (m), GM (SD)	164.31 (1.06)	169.32 (1.06)	159.35 (1.04)	164.94 (1.06)	169.45 (1.06)	159.85 (1.04)

Note. BMI = body mass index. GM = geometric mean. Max = maximum. Min = minimum. SD = standard deviation. Me-PFOSA-AcOH = 2-(N-methyl-perfluoroctane sulfonamido) acetic acid. PFDeA = perfluorodecanoic acid. PFUA = perfluoroundecanoic acid.

2011-2012 sample compared to the 2013-2014 sample were 0.10 ng/mL (*SD* = 1.77) and 0.09 ng/mL (*SD* = 1.62) for PFUA; 0.15 ng/mL (*SD* = 1.74) and 0.13 ng/mL (*SD* = 1.88) for PFDeA; 0.12 ng/mL (*SD* = 2.38) and 0.11 ng/mL (*SD* = 2.10) for Me-PFOSA-AcOH, respectively. The percentage of detected PFAS in serum was larger in the 2011-2012 dataset than in 2013-2014 (PFUA: 41.11% vs. 20.93%; PFDeA: 77.00% vs. 69.48%; Me-PFOSA-AcOH: 54.01% vs. 43.02%). The maximum detected concentrations of PFUA and PFDeA were higher in 2013-2014, with the exception of Me-PFOSA-AcOH which decreased from a maximum of 3.29 ng/mL in 2011-2012 to 2.00 ng/mL in 2013-2014. In general, males tended to have larger mean values and a greater percentage of detected PFAS as compared to females regardless of survey year. Table 1 displays the average weight, waist circumference, BMI, and height of participants which were very similar across the survey years. In the combined, weighted sample for years 2011-2016 (N = 875), the geometric means and standard errors of PFUA, Me-PFOSA-AcOH, and PFDeA were 0.085 (0.002) ng/mL, 0.125 (0.006) ng/mL, and 0.127 (0.004) ng/mL, respectively. PFAS values ranged from 0.07 - 1.7 ng/mL for PFUA, 0.06 - 3.29 ng/mL for Me-PFOSA-AcOH, and 0.07 - 2.20 ng/mL for PFDeA (refer to supplement).

3.2. Analysis

In Table 2, the initial results indicated that male adolescents with detectable levels of PFDeA (≥0.10 ng/mL) had significantly lower waist circumference ($GM_{detected}$ = 79.79 cm, $GM_{undetected}$ = 92.97 cm, p = 0.002) and BMI ($GM_{detected}$ = 23.02, $GM_{undetected}$ = 27.81, $p < 0.001$) in 2011-2012 as well as in 2013-2014 (waist circumference: $GM_{detected}$ = 81.08 cm, $GM_{undetected}$ = 87.83 cm, p = 0.007; BMI: $GM_{detected}$ = 23.36, $GM_{undetected}$ = 25.44, p = 0.026). In 2011-2012 survey years, weight was also significantly reduced in males with detected PFDeA ($GM_{detected}$ = 65.91 kg, $GM_{undetected}$ = 80.16 kg, p = 0.002); however in 2013-2014, the p-value of the coefficient just missed significance, $GM_{detected}$ = 67.00 kg, $GM_{undetected}$ = 73.24 kg, p = 0.058. For males in both survey cycles, waist circumference, weight, and BMI were nonsignificantly reduced in association with detected PFUA. Regarding Me-PFOSA-AcOH, there was no clear trend of increased or decreased anthropometrics in male adolescents.

In females (Table 3), it was illustrated that waist circumference (2011-2012: $GM_{detected}$ = 78.29 cm, $GM_{undetected}$ = 84.05 cm, p = 0.039; 2013-2014: $GM_{detected}$ = 77.40 cm, $GM_{undetected}$ = 83.96 cm, $p < 0.01$) and weight (2011-2012: $GM_{detected}$ = 58.07 kg, $GM_{undetected}$ = 64.70 kg, p = 0.041; 2013-2014: $GM_{detected}$ = 57.20 kg, $GM_{undetected}$ = 65.46 kg, p = < 0.01) were significantly reduced in both survey cycles related to detectable PFDeA exposure. Female adolescents with detected PFDeA were significantly shorter ($GM_{detected}$ = 158.70 m, $GM_{undetected}$ = 161.10 m, p = 0.046) in the 2011-2012 dataset but not in 2013-2014, $GM_{detected}$ = 159.80 m, $GM_{undetected}$ = 160.00 m, p = 0.838. Female BMI was significantly lower in the 2013-2014 survey years, but not in 2011-2012. Females with detectable PFUA

Table 2. Results of *t*-test comparing average adolescent anthropometrics of participants (12 - 18 years) with PFAS levels above and below the LLOD in males from 2011-2012 and 2013-2014 NHANES.

Body measure	2011-2012 Males (N = 145)				p	2013-2014 Males (N = 185)				p
	Detected		Undetected			Detected		Undetected		
	GM	95% CI	*GM*	95% CI		*GM*	95% CI	*GM*	95% CI	
PFUA										
Waist circumference	79.59	(76.05, 83.30)	83.81	(80.25, 87.53)	0.119	80.35	(76.52, 84.37)	83.72	(81.13, 86.38)	0.207
Weight	66.13	(61.21, 71.44)	69.95	(65.64, 74.54)	0.269	66.52	(61.32, 72.16)	69.37	(66.06, 72.86)	0.413
BMI	23.11	(21.67, 24.65)	24.37	(23.03, 25.79)	0.229	23.27	(21.82, 24.80)	24.13	(23.18, 25.12)	0.384
Height	169.20	(166.80, 171.60)	169.40	(167.40, 171.50)	0.872	169.10	(165.80, 172.40)	169.60	(168.00, 171.10)	0.766
PFDeA										
Waist circumference	**79.79**	**(77.28, 82.31)**	**92.97**	**(85.01, 101.70)**	**0.002**	**81.08**	**(78.73, 83.49)**	**87.83**	**(83.05, 92.88)**	**0.007**
Weight	**65.91**	**(62.57, 69.42)**	**80.16**	**(71.21, 90.24)**	**0.002**	67.00	(63.88, 70.27)	73.24	(67.23, 79.78)	0.058
BMI	**23.02**	**(22.05, 24.03)**	**27.81**	**(24.78, 31.20)**	**<0.001**	**23.36**	**(22.48, 24.27)**	**25.44**	**(23.69, 27.31)**	**0.026**
Height	169.20	(167.50, 171.00)	169.80	(166.30, 173.40)	0.771	169.40	(167.60, 171.10)	169.70	(167.30, 172.10)	0.826
Me-PFOSA-AcOH										
Waist circumference	83.84	(80.11, 87.74)	79.89	(76.54, 83.38)	0.139	82.76	(79.55, 86.10)	83.13	(80.15, 86.23)	0.869
Weight	69.25	(64.84, 73.96)	67.36	(62.53, 72.56)	0.581	68.47	(64.17, 73.07)	68.96	(65.25, 72.88)	0.869
BMI	24.31	(22.91, 25.81)	23.29	(21.93, 24.72)	0.321	23.75	(22.56, 25.00)	24.10	(23.01, 25.25)	0.669
Height	168.80	(166.60, 170.90)	170.10	(167.80, 172.40)	0.408	169.80	(167.70, 171.90)	169.20	(167.30, 171.00)	0.652

Note. BMI = body mass index. CI = confidence interval. GM = geometric mean. LLOD = lower limit of detection. Me-PFOSA-AcOH = 2-(N-methyl- perfluoroctane sulfonamido) acetic acid. PFDeA = perfluorodecanoic acid. PFUA = perfluoroundecanoic acid. Results in bold were significant at $p < 0.05$.

Table 3. Results of *t*-test comparing average adolescent anthropometrics of participants (12 - 18 years) with PFAS levels above and below the LLOD in females from 2011-2012 and 2013-2014 NHANES.

Body measure	2011-2012 Females (N = 142)				p	2013-2014 Females (N = 159)				p
	Detected		Undetected			Detected		Undetected		
	GM	95% CI	*GM*	95% CI		*GM*	95% CI	*GM*	95% CI	
PFUA										
Waist circumference	**75.99**	**(73.17, 78.92)**	**82.86**	**(79.32, 86.56)**	**0.003**	**75.69**	**(72.05, 79.52)**	**80.44**	**(78.27, 82.67)**	**0.048**
Weight	**56.48**	**(53.051, 60.13)**	**62.46**	**(58.48, 66.71)**	**0.033**	55.69	(51.15, 60.62)	60.81	(58.19, 63.56)	0.079
BMI	**22.38**	**(21.14, 23.70)**	**24.48**	**(23.10, 25.95)**	**0.033**	21.86	(20.29, 23.56)	23.78	(22.87, 24.74)	0.058
Height	158.90	(157.20, 160.50)	159.70	(158.40, 161.10)	0.416	159.60	(157.80, 161.40)	159.90	(158.80, 161.10)	0.817
PFDeA										
Waist circumference	**78.29**	**(75.79, 80.86)**	**84.05**	**(78.38, 90.12)**	**0.039**	**77.40**	**(75.45, 79.40)**	**83.96**	**(79.89, 88.24)**	**0.005**
Weight	**58.07**	**(55.16, 61.13)**	**64.70**	**(58.49, 71.56)**	**0.041**	**57.20**	**(54.79, 59.71)**	**65.46**	**(60.60, 70.72)**	**0.001**
BMI	23.05	(22.00, 24.15)	24.93	(22.81, 27.24)	0.099	**22.41**	**(21.58, 23.26)**	**25.58**	**(23.88, 27.40)**	**0.001**
Height	**158.70**	**(157.50, 159.90)**	**161.10**	**(159.00, 163.20)**	**0.046**	159.80	(158.60, 161.00)	160.00	(158.30, 161.70)	0.838

Continued

Me-PFOSA-AcOH										
Waist circumference	80.89	(77.53, 84.39)	78.70	(75.33, 82.22)	0.371	**76.56**	**(73.76, 79.47)**	**81.37**	**(78.88, 83.93)**	**0.015**
Weight	61.81	(58.07, 65.80)	57.80	(53.95, 61.93)	0.153	**56.69**	**(52.98, 60.66)**	**61.79**	**(58.93, 64.78)**	**0.034**
BMI	24.02	(22.71, 25.41)	23.07	(21.69, 24.54)	0.338	**22.02**	**(20.74, 23.39)**	**24.30**	**(23.31, 25.32)**	**0.006**
Height	160.40	(158.90, 161.90)	158.30	(156.90, 159.70)	0.044	160.40	(158.80, 162.00)	159.50	(158.2, 160.7)	0.353

Note. BMI = body mass index. CI = confidence interval. GM = geometric mean. LLOD = lower limit of detection. Me-PFOSA-AcOH = 2-(N-methyl-perfluoroctane sulfonamido) acetic acid. PFDeA = perfluorodecanoic acid. PFUA = perfluoroundecanoic acid. Results in bold were significant at $p < 0.05$.

also showed significantly smaller waist circumference in both survey cycles, but only 2011-2012 depicted significantly reduced weight and BMI. Females above the LLOD for Me-PFOSA-AcOH had significantly smaller waist circumference, weight, and BMI, but only in 2013-2014.

Multivariate regression also depicted significantly decreased female waist circumference alongside increasing PFUA concentrations in both survey cycles (2011-2012: $\beta = -0.05$; 95% CI, −0.1060, −0.0004; 2013-2014: $\beta = -0.06$; 95% CI, −0.106, −0.005). Additionally, there was an inverse association between PFUA and female weight-for-age (WAZ) and BMI-for-age z-scores (BMIZ) which was only significant in 2013-2014 survey years (Table 5), WAZ: $\beta = -0.40$; 95% CI, −0.74, −0.05; BMIZ: $\beta = -0.48$; 95% CI, −0.86, −0.10. Overall, PFDeA showed significantly strong, inverse relationships with waist circumference, weight-for-age z-score, and BMI-for-age z-score; however, in 2011-2012 (Table 4) the results were driven by males whereas in 2013-2014 (Table 5) they were driven by females. The regression analysis did not show any significant relationships between Me-PFOSA-AcOH and any of the anthropometric outcomes. The change in height did not appear to be meaningful in relation to any of the PFAS that were evaluated. In the 2011-2016 combined survey years (refer to supplemental material https://health.usf.edu/publichealth/ceoram/research-and-publications), waist circumference and BMI-for-age z-score were both significantly, inversely associated with PFUA and PFDeA in each sex, and in the overall regression analysis when holding all other predictors constant (Table 4 supplemental material). With both sexes combined, an inverse relationship was found between PFUA ($\beta = -0.28$; 95% CI, −0.43, −0.13) and PFDeA ($\beta = -0.29$; 95% CI, −0.43, −0.15) with weight-for-age z-score. This association was significant in males (PFUA $\beta = -0.31$; 95% CI, −0.49, −0.12; PFDeA $\beta = -0.34$; 95% CI, −0.51, −0.16), but not females. Regressing height-for-age z-score onto increasing PFDeA concentrations was significant overall ($\beta = -0.15$; 95% CI, −0.28, −0.03), and this appeared to be driven entirely by female adolescents ($\beta = -0.19$; 95% CI: −0.35, −0.03). Coefficients for Me-PFOSA-AcOH did not demonstrate a meaningful relationship with any of the body measures outcomes studied in the aggregate sample of years 2011-2016. None of the gender interaction terms were significant for any of the PFAS that were evaluated.

Table 4. Adjusted regression coefficients with 95% confidence intervals for selected PFAS and body measures from NHANES 2011-2012.

Body measure	PFUA	PFDeA	Me-PFOSA-AcOH
	β (95% CI)	β (95% CI)	β (95% CI)
Waist circumference[a]	−0.036 (−0.076, 0.003)	−0.07 (−0.11, −0.03)***	0.004 (−0.021, 0.029)
Males	−0.02 (−0.08, 0.04)	−0.08 (−0.14, −0.02)**	0.003 (−0.032, 0.038)
Females	−0.05 (−0.11, −0.00)*	−0.04 (−0.10, 0.01)	−0.01 (−0.05, 0.03)
Weight-for-age Z-score[b]	−0.19 (−0.44, 0.07)	−0.35 (−0.61, −0.09)**	0.04 (−0.13, 0.20)
Males	−0.19 (−0.57, 0.18)	−0.49 (−0.88, −0.11)*	−0.06 (−0.29, 0.17)
Females	−0.13 (−0.48, 0.21)	−0.09 (−0.44, 0.26)	0.10 (−0.14, 0.35)
BMI-for-age Z-score[c]	−0.18 (−0.44, 0.08)	−0.37 (−0.63, −0.11)**	0.01 (−0.15, 0.17)
Males	−0.09 (−0.48, 0.30)	−0.44 (−0.84, −0.05)*	−0.07 (−0.31, 0.16)
Females	−0.26 (−0.61, 0.09)	−0.25 (−0.60, 0.10)	0.12 (−0.12, 0.37)
Height-for-age Z-score[d]	−0.15 (−0.36, 0.06)	−0.07 (−0.29, 0.14)	0.05 (−0.08, 0.18)
Males	−0.21 (−0.52, 0.09)	−0.08 (−0.40, 0.24)	−0.03 (−0.21, 0.16)
Females	−0.04 (−0.33, 0.25)	−0.03 (−0.32, 0.26)	0.20 (0.01, 0.40)

Note. BMI = body mass index. CI = confidence interval. N = sample size. Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamido) acetic acid. PFDeA = perfluorodecanoic acid. PFUA = perfluoroundecanoic acid. Coefficients represent change in dependent variable per 1 ln-unit of each perfluoroalkyl substance. a. Adjusted for age, sex, race/ethnicity, height. b. Adjusted for sex, race/ethnicity, height. c. Adjusted for sex, race/ethnicity. d. Adjusted for sex, race/ethnicity, weight. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 5. Adjusted regression coefficients with 95% confidence intervals for selected PFAS and body measures from NHANES 2013-2014.

Body measure	PFUA	PFDeA	Me-PFOSA-AcOH
	β (95% CI)	β (95% CI)	β (95% CI)
Waist circumference[a]	−0.03 (−0.07, 0.01)	−0.04 (−0.07, −0.01)**	−0.02 (−0.04, 0.01)
Males	−0.005 (−0.061, 0.052)	−0.02 (−0.06, 0.02)	−0.003 (−0.039, 0.033)
Females	−0.056 (−0.106, −0.005)*	−0.06 (−0.10, −0.02)**	−0.034 (−0.065, −0.003)
Weight-for-age Z-score[b]	−0.25 (−0.50, 0.00)	−0.26 (−0.44, −0.08)	−0.08 (−0.24, 0.07)
Males	−0.11 (−0.48, 0.25)	−0.17 (−0.43, 0.08)	0.02 (−0.21, 0.25)
Females	−0.40 (−0.74, −0.05)*	−0.38 (−0.64, −0.12)**	−0.21 (−0.42, −0.00)
BMI-for-age Z-score[c]	−0.24 (−0.51, 0.02)	−0.24 (−0.42, −0.05)*	−0.11 (−0.27, 0.05)
Males	−0.04 (−0.41, 0.32)	−0.10 (−0.35, 0.16)	−0.01 (−0.25, 0.22)
Females	−0.48 (−0.86, −0.10)*	−0.45 (−0.73, −0.16)**	−0.22 (−0.45, 0.02)
Height-for-age Z-score[d]	−0.11 (−0.34, 0.11)	−0.09 (−0.25, 0.07)	0.08 (−0.06, 0.21)
Males	−0.22 (−0.55, 0.10)	−0.15 (−0.38, 0.07)	0.06 (−0.15, 0.27)
Females	0.07 (−0.24, 0.37)	0.05 (−0.19, 0.28)	0.08 (−0.11, 0.26)

Note. BMI = body mass index. CI = confidence interval. N = sample size. Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamido) acetic acid. PFDeA = perfluorodecanoic acid. PFUA = perfluoroundecanoic acid. Coefficients represent change in dependent variable per 1 ln-unit of each perfluoroalkyl substance. a. Adjusted for age, sex, race/ethnicity, height. b. Adjusted for sex, race/ethnicity, height. c. Adjusted for sex, race/ethnicity. d. Adjusted for sex, race/ethnicity, weight. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

4. Discussion

This analysis adds to the extant literature regarding the possible effects of PFAS with a focus on adolescent anthropometric outcomes. The results produced here reflect those of other studies which depict reduced adiposity associated with PFDeA and PFUA in infants, but demonstrates that these exposures may be relevant to adolescent body measures as well [15] [16] [17] [30]. The general lack of consistency with the effects of gender in this data is similar to the contradictory results found in other studies. Wang *et al.* (2016) described reduced average weight and height z-scores between birth and 11 years of age in females with gestational PFDeA and PFUA exposure as measured by maternal third trimester levels; however, the associations with weight did not show a consistent trend as the children aged, so it is likely that the observed effects of reduced weight z-score in relation to gestational exposure do not persist beyond birth [30]. Furthermore, results were limited to females only, as males had no significant association with reduced birthweight nor smaller childhood height and weight z-score for the given sample. A study that detected PFDeA and PFUA in children's own serum found no association with weight at 2 years of age or weight change from birth to 2 years [29]. However, serum collected from young adults has shown significant associations between PFUA and reduced BMI z-score [40]. It is also relevant to consider that the study design may influence the direction of observed outcomes. For example, Karlsen *et al.* (2017) illustrated that cross-sectionally, children's PFDeA, PFOA, and PFNA levels showed significant inverse associations with BMI z-score at 5 years of age, but maternal serum PFOA was positively and significantly associated with increased risk for overweight in children at 5 years follow up [23].

A mechanism of action regarding the purported effects on adiposity in individuals with higher exposures to PFAS may relate to the peroxisome proliferator-activated receptor alpha (PPAR-α). PPAR-α is essential for directing fatty acid oxidation and increasing lipid metabolism [41]. Laboratory studies have shown that PFOS and PFOA can serve as ligands, binding to PPAR-α in human and mouse cell lines *in vitro* [42] [43]. Using HepaRG human hepatic cell lines, it was also demonstrated that PFOA, PFOS, and PFNA are associated with the induction of PPAR target genes [44]. PFAS binding to PPAR-α could theoretically result in the increased catabolism of fatty acids thereby leading to decreased weight outcomes in humans [45]. However, the level of PFAS exposure required for PPAR-α activation may be much higher than what the general human population encounters [46], and natural fatty acids such as those which can be obtained from diet may have a more potent interaction with these nuclear receptors [42]. Furthermore, it has been demonstrated that mice are more susceptible to PPAR-α activation than humans [43] [46], so studies using nonhuman cell lines may not be directly comparable.

Due to their resemblance to fatty acids, PFAS have also been implicated in impacting human triglycerides, although the results have either been conflicting

or null. An *in vitro* laboratory study indicated that the introduction of PFOS, PFOA, and PFNA in human liver cells resulted in statistically significant increases in triglycerides through the induction of genes involved in triglyceride synthesis [44]. In humans, significant positive associations with triglycerides were observed with increasing PFOS and PFOA in overweight children between 8 - 10 years [28]; however, significant inverse associations with triglycerides in obese female adults with increasing PFOS concentrations has also been described [47]. Other cross-sectional analyses have found no associations between triglycerides and PFOS, PFNA, PFHxS, PFDeA, and PFUA [40] [48] [49]. In a prospective study, elevated triglycerides were found to be related to increasing PFDeA and PFNA in a dose-dependent manner, as measured in third trimester serum from pregnant women [11]; however, associations between Me-PFOSA-AcOH, PFOS, PFOA, and PFHxS and triglycerides were nonsignificant, and with the cohort being restricted to females only, the results are not generalizable.

Since perfluoroalkyl chemicals may affect adiposity and lipid metabolism as potential endocrine disruptors, some studies have evaluated PFAS exposure as it relates to cholesterol levels. Greater serum PFOS and PFOA were significantly related to higher concentrations of total cholesterol and LDL in individuals who drank contaminated water issued from a West Virginia manufacturing facility [50] [51], and in a Swedish population living near a military airport that used PFAS-containing firefighting foam [52]. However, it is unknown whether the observed increases in cholesterol occurred before or after the increase in perfluoroalkyl consumption in these studies. This issue of temporality was addressed by Fitz-Simon *et al.* (2013) who reported that in the years following water filtration to reduce PFAS levels, West Virginia and Ohio residents whose PFOA and PFOS concentrations decreased by half also experienced a significant associated decrease in LDL and total cholesterol [53]. Results of other studies have illustrated increased PFOS related to higher total cholesterol [11] [54] [55] and LDL cholesterol [40], and greater serum PFOA associated with increasing total cholesterol [40] [49] [54] [55] [56]. However, it should be noted that the study by Koshy *et al.* (2017) involved a cohort of New York schoolchildren exposed to myriad air pollutants generated from the September 11th World Trade Center collapse; therefore, other inhaled contaminants may or may not have influenced the observed outcomes [40]. Other studies have found no meaningful evidence of a relationship between total cholesterol and serum PFOA in pregnant U.S. and Norwegian women [11] [57]. Likewise, in the Canadian Health Measures Survey (CHMS) which is structured similar to the U.S. NHANES, no significant relationships were found between PFOS or PFOA with LDL or total cholesterol [48].

With cross-sectional analyses, it is impossible to determine a causal relationship between the three PFAS studied and body measures. The analysis was restricted to only including the variables available from the NHANES questionnaires which may not include all the relevant explanatory risk factors for BMI, weight, waist circumference, and height. Furthermore, it is possible that other

unmeasured chemical exposures could explain the effects on anthropometrics that were observed. For example, information regarding birth weights and maternal smoking were not provided for participants over the age of 15, so these factors could not be assessed for the adolescents sampled in this analysis. Additionally, questionnaires by nature are subject to response bias from the participants, including recall bias that could lead to misclassification of covariates.

However, the strength of this analysis was that the anthropometrics (weight, waist circumference, BMI, and height) were measured by trained health professionals in the Mobile Examination Center (MEC) rather than relying on self-reporting, which has been done in other studies. Although temporality could not be established in a cross-sectional design, a trend in reduced body measures outcomes was able to be described in the individual sample years as well as the combined, weighted sample. Also, this study adds additional insight into the potential effects of three PFAS that have not been reviewed extensively.

Although human serum concentrations of PFAS have been declining since 2002, it is still relevant to investigate the potential biological effects of these chemicals to determine how they may impact human developmental outcomes. Taken together, the results of this analysis and others indicate that higher levels of PFAS exposure may be related to weight outcomes, but continued research is needed to determine what other factors may influence the disparate results reported across studies.

5. Conclusions

In NHANES 2011-2012, males aged 12 - 18 had significantly decreased waist circumference, weight-for-age, and BMI-for-age z-scores associated with increasing PFDeA levels. In NHANES 2013-2014, females between the ages of 12 and 18 had significantly reduced waist circumference, weight-for-age z-score, and BMI-for-age z-score correlated with increasing PFUA and PFDeA concentrations. After controlling for age, sex, race/ethnicity, and weight, there were no significant associations between height and any of the PFAS that were evaluated. The adjusted models did not illustrate a meaningful relationship between Me-PFOSA-AcOH and any of the anthropometric outcomes for these samples.

Tests from combined sample years (2011-2016) determined that in males between the ages of 12 and 18, detectable serum concentrations of PFUA and PFDeA may be responsible for attenuated weight. Waist circumference and BMI-for-age z-score were reduced in both sexes with increasing levels of PFUA and PFDeA. Although shorter average height and height-for-age z-score were associated with higher concentrations of PFDeA in females in the full sample, these results were not reflected in the separate regression analyses for years 2011-2012 or 2013-2014.

Acknowledgements

This article is supported in part by Center for Environmental and Occupational Risk Analysis and Management, College of Public Health, University of South

Florida, Tampa, Florida.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix A. Supplementary Material

Supplementary data for this article can be accessed online at: https://health.usf.edu/publichealth/ceoram/research-and-publications.