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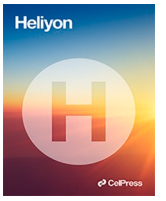

Research article

Sex and obesity influence the relationship between perfluoroalkyl substances and lean body mass: NHANES 2011–2018

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ABSTRACT

Objective: Polyfluoroalkyl substances (PFAS) are known endocrine disruptors, that have been the subject of limited research regarding their impact on human lean body mass. The aim of this study was to investigate the effects of PFAS exposure on lean body mass.
Methods: We performed a cross-sectional data analysis involving 1022 adolescents and 3274 adults from the National Health and Nutrition Examination Survey (NHANES) 2011–2018, whose lean body mass was measured by dual-energy X-ray absorptiometry. The lean mass index (LMI) was calculated as lean body mass dividing by the square of height. The association between PFAS and LMI was examined through a multivariate-adjusted weighted generalized linear model. Moreover, weighted quantile sum (WQS) regression models were employed to futher examine the relationship between the mixture of PFAS and LMI.
Results: Regression analyses revealed an inverse correlation between PFAS exposure and LMI after adjusting for potential covariates. Adults with higher serum PFAS concentrations manifested a reduction in whole LMI ($\beta = -0.193$, 95 % confidence interval (CI): −0.325 to −0.06). Notably, this correlation was particularly significant in adult females and individuals with obesity, and it was observed across diverse anatomical regions, including lower limbs, right arm, trunk, and whole lean body mass. In adult females, the association between PFAS and whole LMI was statistically significant ($\beta = -0.294$, 95 % CI: −0.495 to −0.094), and a similar trend was found in obese individuals ($\beta = -0.512$, 95 % CI: −0.762 to −0.261). WQS regression analyses supported the results obtained from weighted linear regression analyses.
Conclusions: Our study suggests that exposure to PFAS, whether individually or in combination, is associated with decreased lean body mass in specific body areas, with sex and obesity serving as major influencing factors.

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Abbreviations

ALMI	Arm lean mass index
BCA	Body composition analysis
BMI	Body mass index
CDC	Center for Disease Control
CI	Confidence interval
DXA	Dual-energy X-ray Absorptiometry
EPA	Environmental Protection Agency
ER	Estradiol receptor
GH-IGF	Growth hormone-insulin-like growth factor
HLMI	Head lean mass index
LALMI	Left arm lean mass index
LLLMI	Left leg lean mass index
LLMI	Leg lean mass index
LMI	Lean mass index
Me-PFOSA-AcOH	2-(N-Methyl-perfluorooctane sulfonamido) acetic acid
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PFAA	Perfluoroalkyl acids
PFAS	Polyfluoroalkyl substances
PFDeA	Perfluorodecanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoate
PFOS	Perfluorooctane sulfonate
PFUA	Perfluoroundecanoic acid
PPAR	Peroxisome proliferator-activated receptor
RALMI	Right arm lean mass index
RLLMI	Right leg lean mass index
SPE-HPLC-TIS-MS/MS	Solid phase extraction and high-performance liquid chromatography-turbo ion spray coupled ionization-tandem mass spectrometry
TLMI	Trunk lean mass index
WHO	World Health Organization
WLMI	Whole lean mass index
WQS	Weighted quantile sum

1. Introduction

Perfluoroalkyl substances (PFAS) are a group of synthetic chemicals characterized by the substitution of hydrogen atoms with fluorine atoms [1]. Due to their hydrophobic and oleophobic properties, PFAS are extensively employed in the manufacture of household and industrial goods [2], including surfactants, fire-fighting foams, and textile treatments. Non-occupationally exposed populations primarily encounter PFAS through consumption of contaminated food and drinking water [3]. PFAS are notorious for their environmental persistence and ability to accumulate in living organisms [4], leading to long-term retention in human tissues, with half-lives ranging from 3.8 to 7.3 years [5–7]. According to the National Health and Nutrition Examination Survey (NHANES) 2017–2018, perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonic acid (PFHxS) were found in the blood over 98 % U.S. population. Among several PFAS present in human blood, PFOS has the highest median serum concentration at 4.3 μg/L.

PFAS, a group of typical endocrine-disrupting chemicals [8,9] has been shown to potentially decrease lean mass by reducing anabolic hormone levels both in human and mouse models. Lean body mass serves as a valuable metric for assessing muscle function and nutritional status, and its role in maintaining metabolic homeostasis is well established [10]. Studies have demonstrated that low lean body mass correlates with an elevated risk of metabolic syndrome, diabetes, and cardiovascular mortality [11–14]. Furthermore, it has been demonstrated that higher levels of whole lean body mass gain can help mitigate the development of metabolic syndrome and cardiovascular disease [15].

However, research on PFAS and its impact on lean body mass in adolescents and adults has yielded conflicting results. A longitudinal child health cohort study [16] discovered that higher serum concentrations of PFAS were associated with a decrease in lean body mass accumulation from mid-childhood to early adolescence. This effect may be influenced by sex and race. Conversely, another prospective study [17] focusing on middle-aged individuals (aged 50 years) demonstrated a negative correlation between PFHxS and whole lean mass as well as leg lean mass in men but not in women. Additionally, a study using NHANES 2011–2018 found a positive

association between PFHxS and lean body mass in adolescents aged 12–18 years [18].

Given the lack of established associations between PFAS exposure and human lean body mass, current research is limited by small sample sizes and varied assessment methods. Many studies have used bioelectrical impedance analysis (BIA) instead of the gold standard Dual-energy X-ray Absorptiometry (DXA). DXA is widely recognized for its accuracy, reproducibility, and discrete cutoff values of DXA, and existing studies have shown that BIA tends to overestimate lean body mass compared with DXA [19]. In addition, a significant portion of recent studies have focused on vulnerable populations [20–22], specifically pregnant women and infants, which limits the generalizability of findings. The limitations of the sample also make it challenging to conduct stratified analyses to investigate the potential differences in the health effects of PFAS exposure on lean body mass across different age groups, sexes, and obesity levels.

Therefore, this study utilized nationally representative data from NHANES 2011–2018 to investigate the association between PFAS exposure and lean body mass. The study employed stratified analysis by age, sex, and obesity level to explore the potential health risks associated with co-exposure to multiple PFAS. This research aim to contribute additional evidence to the existing body of knowledge.

2. Methods

2.1. Study population

NHANES is a regular cross-sectional and nationally representative survey of US population conducted by the National Center for Health Statistics (NCHS) since 1999. The survey protocol was approved by the Research Ethics Review Board of the NCHS. Detailed descriptions of NHANES including study design, protocol, data collection methods and data access are publicly available (https://www.cdc.gov/nchs/nhanes).

For this study, data from four cycles (NHANES 2011–2018) were utilized. Among the 39156 participants recruited during NHANES 2011–2018, 5074 subjects had both lean body mass data accessed by DXA and serum PFAS measurements. After excluding individuals with missing covariates, we finally included 1022 adolescents (aged 12–19 years) and 3274 adults (aged over 19 years) in the analysis. The screening procedure for the study population is summarized in Fig.A.1.

2.2. PFAS measurements

PFAS wwere quantitatively detected in a subsample of one-third of the population over a span of 12 years (from 2011 to 2018) in NHANES using online solid phase extraction and high-performance liquid chromatography-turbo ion spray coupled with ionization-tandem mass spectrometry (online SPE-HPLC-TIS-MS/MS). Serum samples were prepared, refrigerated, and transported to the lab of the National Center for Environmental Health for detection following a standard operation protocol. Seven PFAS congeners [Perfluorodecanoic acid (PFDeA), PFHxS, Perfluorononanoic acid (PFNA), 2-(N-methylperfluoroctanesulfonamido) acetic acid (Me-PFOSA-AcOH), PFOA, Perfluoroundecanoic acid (PFUA) and PFOS] that are available through 2011 to 2018 were included in our analysis. The lower limit of detection (LLOD) ranged from 0.08 to 0.2 ng/ml and those below the LLOD were assigned an amount equal to LLOD divided by square root of 2 (LLOD/sqrt (2)).

2.3. Lean body mass assessments

DXA is a reliable modality that utilizes X-rays to quantify bone mineral density and soft tissue composition in various anatomical regions, including the whole body, bilateral upper and lower limbs, trunk, and head. These measurements were obtained by certified and experienced radiologists using the Apex software program on a Hologic Discovery Model A densitometer (Hologic, Inc., Bedford, MA). NHANES employed multiple imputations to estimate DXA measures for missing data. As suggested, we excluded subjects with highly variable imputed DXA measures from our analysis. Additionally, the NHANES body composition analysis (BCA) option was enabled for body scan analysis, which adds 5 % of lean body mass to fat mass. For more details on working with sample weights and other analytical issues, please refer to the NHANES Survey Methods and Analytic Guidelinesand the online NHANES Tutorial.

2.4. Covariates

The selection of covariates was based on previous studies on PFAS [23,24]. Demographic variables, including age (in years), sex (male and female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black and Other race), ratio of family income to poverty, parental educational attainment, and educational attainment, were obtained from the NHANES database. The ratio of family income to poverty was calculated by dividing household income by the poverty guidelines for a given survey year and served as an indicator of economic status. Parental educational attainment was used as a proxy for adolescents' educational attainment as it is often correlated with age. Additional information on smoking exposure, physical activity, energy intake, and protein intake were collected through questionnaires and examinations. Smoking exposure was assessed using two indicators: whether adolescents had used tobacco products in the past 5 days and whether they lived in a household with smokers. Adult smoking exposure was defined by whether individuals had smoked 100 cigarettes in their lifetime. The World Health Organization (WHO) recommends 60 minutes of physical activity per day for adolescents, which translates to 420 minutes per week. This recommendation was used as a cut-off to assess adolescent physical activity. For adults, the recommendation was 300 minutes per week [25]. Finally, daily energy and protein intake were assessed using the energy and protein supply ratio [26], which were used as indicators of energy and protein intake in

relation to lean body mass.

2.5. Data analysis

The statistical analysis and data representation in this study utilized sophisticated weighting techniques. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means with standard deviations. To account for the complicated sampling design and the non-response phenomenon of NHANES when evaluating serum PFAS substances, the NCHS recommended applying perfluoroalkyl acids (PFAA)-specific subsample weights [27]. Additionally, a natural logarithm(ln) transformation was performed to improve the normality of the data for the convenience of statistical analysis due to its non-normal distribution.

The data were divided into groups based on sex and obesity level for descriptive analysis, considering the differences in lean body mass development by sex. The lean mass index (LMI) was utilized to reflect changes in lean mass due to the influence of lean body mass receptor type. Subgroup analyses based on body mass index (BMI) were also stratified and reiterated according to prior analysis. Adolescents were categorized into normal or overweight/obese according to the recommendations of the Data Table of BMI-for-age Charts by the Center for Disease Control (CDC), while adults were classified as underweight and normal (BMI <25.0 kg/m^2) or overweight and obese (BMI$\geq$25 kg/m^2) according to CDC guidelines. The association between PFAS and lean body mass was systematically examined through a multivariate-adjusted weighted generalized linear model. Furthermore, a linear trend was tested after stratifying the subjects by sex and degrees of obesity. The original p values and 95 % confidence intervals (CI) for the results are provided. Subsequently, the weighted quantile sum (WQS) [28] mixed effect regression was performed separately for different sexes to evaluate both the overall effect of environmental exposure and the contribution of each component in the mixture to the overall effect. In addition, the impact of protein intake and serum albumin on body composition were considered in a sensitivity analysis to test the robustness of the relationship between PFAS and LMI as indicated in previous studies [29,30]. Finally, a WQS index was established based on the quartiles of the seven independent variables.

Table 1
Characteristics of adolescents and adults with PFAS and lean mass in NHANES2011-2018.[a]

Characteristics	Adolescents		p	Adults		p
	Boys	Girls		Males	Females	
Number	543	479	0.01	1617	1657	0.34
Age [yrs, mean (SD)]	15 (0.11)	15 (0.10)	0.30	39 (0.45)	40 (0.51)	0.15
Race/ethnicity [n (%)]						
Mexican	119 (21.92)	104 (21.71)	0.20	221 (13.67)	230 (13.88)	0.12
Other Hispanic	40 (7.37)	50 (10.44)		152 (9.40)	169 (10.20)	
Non-Hispanic White	173 (31.86)	120 (25.05)		614 (37.97)	591 (35.67)	
Non-Hispanic Black	137 (25.23)	116 (24.22)		337 (20.84)	391 (23.60)	
Other Race	74 (13.62)	89 (18.58)		293 (18.12)	276 (16.65)	
Parents/Education level[b]						
Less than high school	131 (24.13)	115 (24.01)	>0.90	293 (18.12)	244 (14.73)	<0.001
High school/GED/AA	313 (57.64)	266 (55.53)		894 (55.29)	916 (55.28)	
College graduate/above	99 (18.23)	98 (20.46)		430 (26.59)	497 (29.99)	
PIR [mean (SD)]	2.52 (0.12)	2.43 (0.12)	0.50	2.98 (0.06)	2.97 (0.06)	>0.9
BMI (kg/m^2)	24.08 (0.37)	24.56 (0.49)	0.60	29.15 (0.21)	29.16 (0.27)	0.04
Energy (kcal)	2235 (54.96)	1678 (28.63)	<0.001	2519 (28.38)	1822 (17.22)	<0.001
Protein (gm)	86.61 (2.67)	60.05 (1.28)	<0.001	98.83 (1.37)	70.48 (0.68)	<0.001
Protein energy supply (%)	0.15 (0.00)	0.15 (0.00)	0.01	0.16 (0.00)	0.15 (0.00)	0.30
Cigarette exposure status						
Exposed	166 (30.57)	144 (30.06)	0.80	709 (43.85)	546 (32.95)	<0.001
Unexposed	377 (69.43)	335 (69.94)		908 (56.15)	1111 (67.05)	
Physically active						
Inadequate	271 (49.91)	365 (76.20)	<0.001	835 (51.64)	1085 (65.48)	<0.001
Adequate	272 (50.09)	114 (23.80)		782 (48.36)	572 (34.52)	
Lean mass index (kg/m^2)						
Trunk	8.15 (0.08)	7.35 (0.10)	<0.001	9.90 (0.06)	8.53 (0.05)	<0.001
Whole	17.16 (0.18)	15.00 (0.20)	<0.001	19.94 (0.12)	16.62 (0.10)	<0.001
Serum PFAS (ng/mL) [mean (SD)][c]						
PFHxS	1.96 (0.18)	1.28 (0.07)	<0.001	2.31 (0.08)	1.12 (0.05)	<0.001
Me-PFOSA-AcOH	0.20 (0.01)	0.17 (0.02)	<0.001	0.16 (0.00)	0.17 (0.00)	>0.90
PFNA	0.72 (0.04)	0.67 (0.04)	0.01	0.79 (0.02)	0.71 (0.02)	<0.001
PFDeA	0.16 (0.00)	0.16 (0.00)	0.80	0.25 (0.01)	0.25 (0.01)	0.07
PFUA	0.09 (0.00)	0.10 (0.01)	0.30	0.17 (0.01)	0.15 (0.01)	0.13
PFOA	1.80 (0.06)	1.49 (0.05)	<0.001	2.37 (0.06)	1.89 (0.15)	<0.001
PFOS	4.42 (0.17)	3.43 (0.13)	<0.001	7.89 (0.22)	4.72 (0.15)	<0.001
$\sum$PFAS	9.38 (0.37)	7.30 (0.25)	<0.001	13.94 (0.31)	9.04 (0.28)	<0.001

[a] Statistics were weighted; adolescents (12–19 years) and adults (>19 years).
[b] Education level: The educational level of young people is directly related to their age, so parental educational level is used as a proxy.
[c] Only those with detection frequencies >40 % were included.

R 4.1.2 Statistical software was used for data analysis, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Descriptive statistics

Table 1 shows the socio-demographic characteristics, body composition-related indices and blood concentrations of PFAS for the study population, categorized by sex and age groups. The population consisted of 1022 adolescents (median age 15 years; 53.13 % boy) and 3274 adults (median age 40 years; 49.39 % male). As expected, adolescents had lower exposure to most PFAS compared to adults. The Spearman's rank correlation coefficients, which assess the relationship between the concentrations of seven chemicals, ranged from 0.06 to 0.93. These correlations should be considered when evaluating their potential association with health outcomes. After stratification, statistically significant differences were found in race, poverty level, dietary intake, PFAS exposure, and LMI among adolescents and adults. Furthermore, additional descriptive statistics revealed significant differences between male and female adolescents and adults, stratified by obesity status.

3.2. Relationship between PFAS and body composition indicators

The associations between PFAS metabolites and LMI by age group were demonstrated in Table 2 and Fig.A.2. Serum PFUA levels were found to be negatively correlated with LMI of left arm, upper limbs, and trunk. Specifically, for each unit increase in ln-transformed PFUA concentration, there was a change of −0.031 (95 % CI: −0.059 to −0.002) in upper limbs LMI and a change of −0.103 (95 % CI: −0.198 to −0.007) in trunk LMI among adolescents. On the other hand, teenagers with higher levels of PFHxS had higher LMI in the upper limbs, lower limbs, trunk and whole regions ($p < 0.05$). Additionally, a significant positive association was observed between head LMI and PFOA, PFOS ($p < 0.05$). However, there was no significant correlation between LMI in different areas of the body and serum concentrations of other PFAS, only weak correlation tendencies were discovered.

In our study involving adult participants, we observed a negative correlation between serum levels of PFDeA, PFOA, total PFAS and both trunk and whole LMI (Table 2 and Fig.A.3). The correlation coefficients between PFDeA, PFOA, PFOS, total PFAS concentrations and trunk LMI were −0.091 (95 % CI: −0.163 to −0.018), −0.087 (95 % CI: −0.177 to 0.003), −0.117 (95 % CI: −0.184 to −0.050),

Table 2
Association between PFAS and lean mass index by age status groups in all participants in NHANES 2011–2018.

PFAS metabolites	HLMI	ALMI	LLMI	TLMI	WLMI
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Adolescent					
PFHxS	0.004 (−0.006, 0.015)	**0.025* (-0.004, 0.053)**	**0.083* (0.009, 0.158)**	**0.137* (0.043, 0.231)**	**0.250* (0.048, 0.452)**
Me-PFOSA-AcOH	0.001 (−0.012, 0.015)	0.024 (−0.005, 0.053)	0.014 (−0.055, 0.084)	0.016 (−0.071, 0.104)	0.044 (−0.138, 0.226)
PFNA	0.006 (−0.004, 0.017)	−0.013 (−0.045, 0.019)	−0.010 (−0.089, 0.068)	−0.037 (−0.136, 0.062)	−0.047 (−0.245, 0.150)
PFDeA	0.005 (−0.008, 0.018)	−0.013 (−0.053, 0.027)	−0.019 (−0.140, 0.103)	−0.053 (−0.174, 0.069)	−0.086 (−0.354, 0.183)
PFUA	0.001 (−0.018, 0.019)	**−0.031* (-0.059, -0.002)**	−0.067 (−0.164, 0.030)	**−0.103* (-0.198, -0.007)**	**−0.187* (-0.370, -0.003)**
PFOA	**0.019* (0.003, 0.035)**	0.010 (−0.048, 0.067)	0.023 (−0.133, 0.179)	−0.004 (−0.177, 0.169)	0.045 (−0.334, 0.423)
PFOS	**0.014* (0.002, 0.025)**	0.012 (−0.027, 0.051)	0.074 (−0.057, 0.205)	0.026 (−0.117, 0.169)	0.158 (−0.158, 0.473)
∑PFAS	0.013 (−0.001, 0.026)	0.016 (−0.030, 0.063)	0.085 (−0.056, 0.227)	0.065 (−0.094, 0.225)	0.208 (−0.143, 0.559)
Adults					
PFHxS	−0.004 (−0.011, 0.003)	0.002 (−0.014, 0.018)	0.002 (−0.034, 0.038)	−0.047 (−0.110, 0.017)	−0.061 (−0.164, 0.041)
Me-PFOSA-AcOH	−0.001 (−0.008, 0.005)	−0.007 (−0.024, 0.009)	−0.017 (−0.060, 0.027)	−0.016 (−0.077, 0.046)	−0.071 (−0.169, 0.027)
PFNA	0.004 (−0.004, 0.012)	−0.001 (−0.021, 0.019)	**−0.039*** (−0.074, −0.003)	−0.065 (−0.141, 0.011)	**−0.117* (-0.239, 0.004)**
PFDeA	0.001 (−0.006, 0.009)	−0.011 (−0.033, 0.011)	**−0.056*** (−0.097, −0.015)	**−0.091* (-0.163, -0.018)**	**−0.151* (-0.274, -0.027)**
PFUA	**0.008* (0.0001, 0.016)**	−0.0001 (−0.021, 0.021)	0.001 (−0.040, 0.041)	−0.016 (−0.074, 0.042)	**−0.026 (-0.136, 0.085)**
PFOA	0.003 (−0.012, 0.006)	−0.006 (−0.032, 0.020)	−0.043 (−0.095, 0.008)	**−0.087* (-0.177, 0.003)**	**−0.138* (-0.279, 0.004)**
PFOS	−0.003 (−0.010, 0.005)	−0.009 (−0.029, 0.011)	**−0.036* (-0.076, 0.003)**	**−0.117* (-0.184, -0.050)**	**−0.172* (-0.275, -0.070)**
∑PFAS	0.003 (−0.012, 0.007)	−0.010 (−0.035, 0.015)	**−0.045* (-0.093, 0.003)**	**−0.121* (-0.207, -0.035)**	**−0.193* (-0.325, -0.060)**

Notes: adolescents (12–19 years) and adult (>19 years). Estimates were presented as coefficients and 95 % confidence intervals (CIs) and were adjusted for age (continuous), gender (categorical), race/ethnicity (categorical), education (categorical), BMI (categorical), ratio of family income to poverty (categorical), smoke expose (categorical), Energy (continuous), Protein energy supply ratio(continuous), physically active(categorical). HLMI: Head lean mass index; ALMI: Arm lean mass index; LLMI: leg lean mass index; TLMI: trunk lean mass index; WLMI: whole lean mass index. *$p < 0.05$.

and −0.121 (95 % CI: −0.207 to −0.035), respectively. Additionally, we observed a significant negative correlation between PFNA and LMI of left leg, lower limbs, as well as between PFDeA and left leg, right leg, and lower limb lean mass ($p < 0.05$).

3.3. Relationship between PFAS and body composition indicators by sex

In the analysis of male adolescents, PFAS showed rare associations with LMI, except for PFHS which consistently correlated positively with trunk and whole LMI (Table A.1 and Fig.A.2). Among female adolescents, PFOA and PFOS showed positive associations with the head LMI while PFUA was negatively linked with LMI of the head, upper limbs, lower limbs, trunk, and whole body significantly.

For adults, the stratified assessment revealed that only PFOA, PFOS, total PFAS, and trunk LMI were adversely associated in continuous modeling for men (Table A.2 and Fig.A.3). However, most PFAS demonstrated relationships in females. The whole lean mass showed a negative correlation with PFOA, PFOS, PFDeA, Me-PFOSA-AcOH, and total PFAS (β = −0.189, 95%CI: −0.365 to −0.012; β = −0.259, 95%CI: −0.417 to −0.102; β = −0.220, 95%CI: −0.411 to −0.029; β = −0.159, 95%CI: −0.299 to −0.020; β = −0.294, 95%CI: −0.495 to −0.094). Additionally, there were apparent negative correlations between Me-PFOSA-AcOH and right arm LMI, and total PFAS, PFOA, PFDeA, and PFOS with lower limbs LMI ($p < 0.05$). Furthermore, right arm LMI showed a negative connection with PFDeA and PFOS, and other PFAS that did not demonstrate a connection also displayed a negative correlation trend in certain regions.

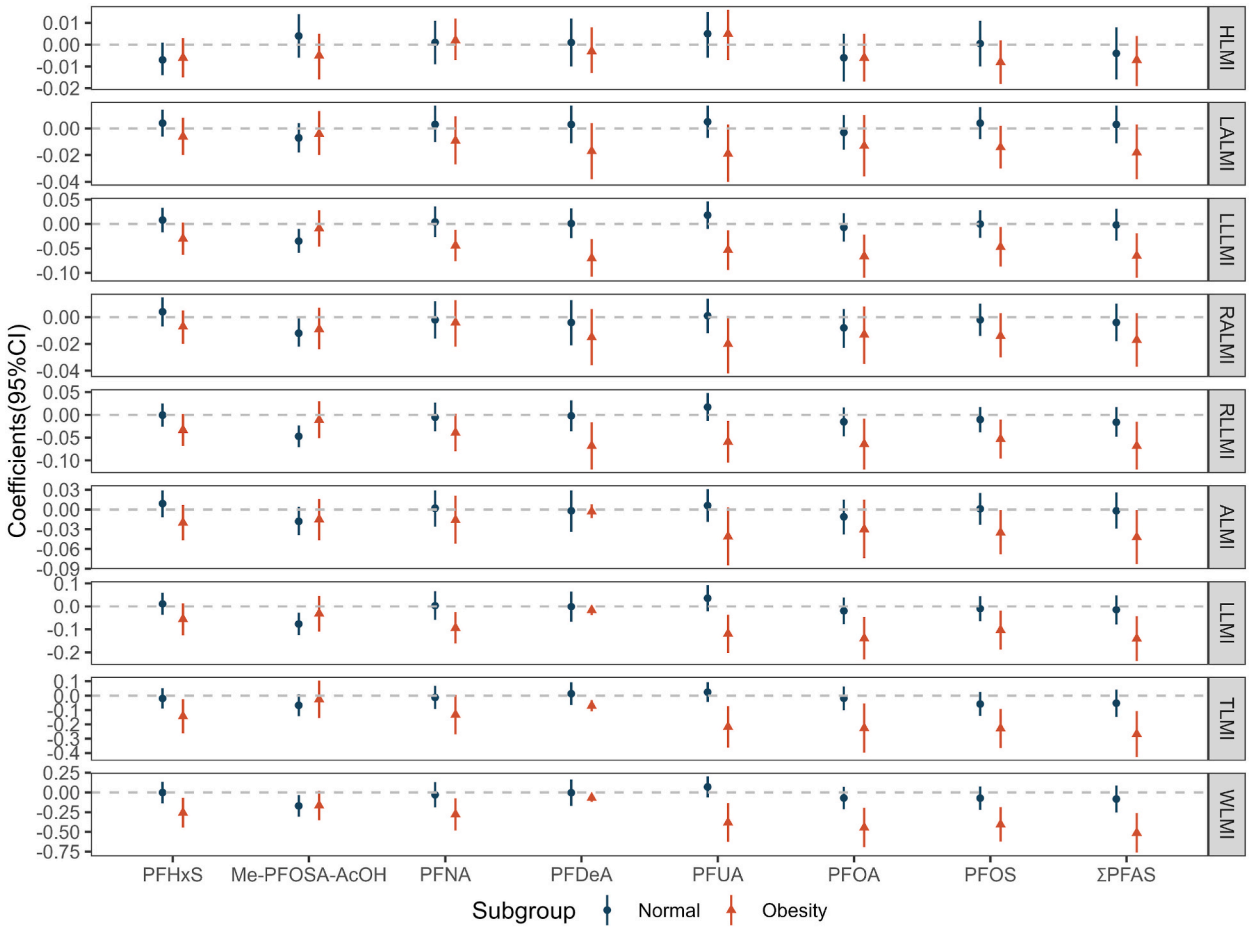

Fig. 1. Associations of quartiles of PFAS with HLMI, LALMI, LLLMI, RALMI, RLLLMI, ALMI, LLMI, TWWI, WLMI in obesity-age groups in participants of >19 years old in NHANES 2011–2018. Obesity status: adults were defined as "normal" if BMI≤25 kg/m^2, otherwise adults' status was defined as "obese". Estimates were adjusted for age (continuous), gender (categorical), race/ethnicity (categorical), education (categorical), BMI category, ratio of family income to poverty (categorical), smoke expose (categorical), Energy (continuous), Protein energy supply ratio(continuous), physically active(categorical). HLMI: Head lean mass index; LALMI: left arm lean mass index; LLLMI: left leg lean mass index; RALMI: right arm lean mass index; RLLMI: right leg lean mass index; TLMI: trunk lean mass index; WLMI: whole lean mass index; CI: confidence interval.

3.4. Relationship between PFAS and body composition indicators by obesity level

Stratified analyses were conducted to examine the impact of obesity on the association between PFAS and lean body mass. Specifically, it was found that PFHxS had a positive correlation with all lean mass components in the normal weight adolescent population, while this correlation was not observed in the adolescent obese population (Table A.3 and Fig.A.4). Additionally, positive correlations were observed between head lean mass and both PFNA (β = 0.014, 95%CI: 0.003 to 0.025) and PFOA (β = 0.031, 95 % CI: 0.009 to 0.053) in normal weight adolescents.

However, in the subgroup of obese adults, a more pronounced negative association between PFAS and LMI was evident. Specifically, PFOA, PFOS, PFDeA, PFNA, PFUA and total PFAS showed a significant negative association with LMI. The correlation coefficients for whole LMI were as follows: β = −0.444, 95 % CI: −0.694 to −0.194 for PFOA; β = −0.405, 95 % CI: −0.623 to −0.187 for PFOS; β = −0.068, 95 % CI: −0.120 to −0.016 for PFDeA; β = −0.277, 95 % CI: 0.481 to −0.073 for PFNA; β = −0.381, 95 % CI: −0.626 to −0.135 for PFUA. Moreover, serum levels of PFUA, PFOA, PFOS, total PFAS and LMI in left leg, right leg, lower limbs, trunk, as well as whole LMI were also significantly negatively correlated ($p < 0.05$). Furthermore, PFNA and PFDeA exhibited unfavorable correlations with the right leg and lower limbs. Finally, a negative correlation was observed between left arm, leg, whole LMI and Me-PFOSA-AcOH in the normal population (Table A.4 and Fig. 1). However, no correlation was found between LMI and Me-PFOSA-AcOH in obese adults.

3.5. Sensitivity analysis

Multivariate-adjusted weighted generalized linear models were re-run in this study after including serum and urine albumin as covariates (Table A.5-A.7). The outcomes derived from the sensitivity analysis demonstrated the robustness of most findings. Specifically, the associations and linear trends between PFDeA, PFUA, PFOS, total PFAS and LMI in obese adult groups, as well as PFDeA, PFOS, total PFAS and LMI in female groups were consistent with our primary results (Table A.7).

3.6. Relationship between WQS indices and body composition for perfluorinated mixtures

The WQS analysis confirmed the findings of the linear regression model. Specifically, in obese teenagers, an inverse association was found between the WQS index and the LMI of right leg (β = −0.077, 95%CI: −0.128 to −0.026) when the WQS negative model was stratified by sex and degree of obesity (Table A.9).

In the WQS analysis of adults, the WQS index was found to be negatively associated with women head LMI (β = −0.003, 95%CI: −0.005 to 0.000) (Table A.10). Conversely, among adult males, both the leg and trunk LMI were inversely correlated with the WQS index. Further investigation of obesity stratification revealed that in the normal population, only the whole LMI was correlated, while in the obese individuals, negative correlations were found with the left leg, right arm, trunk, subtotal, and whole LMI (Table 3).

Table 3
Associations between PFAS and lean mass index by WQS regression model by BMI status groups in >19-year-old participants in NHANES 2011–2018.

Body lean mass index	β	95%CI	*p*
Normal			
HLMI	−0.004	(−0.003, 0.002)	0.7944
LALMI	−0.002	(−0.008, 0.003)	0.5251
LLLMI	0.006	(−0.004, 0.018)	0.3168
RALMI	−0.003	(−0.009, 0.002)	0.3346
RLLMI	−0.011	(−0.025, 0.002)	0.1805
ALMI	−0.004	(−0.012, 0.002)	0.3186
LLMI	0.001	(−0.023, 0.027)	0.9001
TLMI	−0.023	(−0.051, 0.004)	0.1596
WLMI	−0.084	(−0.155, −0.014)	**0.0486**
Obese			
HLMI	−0.002	(−0.006, 0.001)	0.2496
LALMI	−0.005	(−0.012, 0.000)	0.1598
LLLMI	−0.035	(−0.054, −0.015)	**0.0031**
RALMI	−0.012	(−0.018, −0.006)	**0.0011**
RLLMI	−0.016	(−0.035, −0.005)	0.1586
ALMI	−0.014	(−0.027, −0.001)	0.0707
LLMI	−0.031	(−0.063, −0.000)	0.0962
TLMI	−0.099	(−0.142, −0.055)	**0.0001**
WLMI	−0.235	(−0.345, −0.126)	**0.0004**

Notes: Estimates were obtained in WQS regression after adjusting for age (continuous), gender (categorical), race/ethnicity (categorical), education (categorical), BMI (categorical), ratio of family income to poverty (categorical), smoke expose (categorical), Energy (continuous), Protein energy supply ratio(continuous), physically active(categorical). Obesity status was defined as "normal" if BMI≤25 kg/m^2, otherwise adults' status was defined as "obese". HLMI: Head lean mass index; LALMI: left arm lean mass index; LLLMI: left leg lean mass index; RALMI: right arm lean mass index; RLLMI: right leg lean mass index; TLMI: trunk lean mass index; WLMI: whole lean mass index; CI: confidence interval.

Additionally, a negative trend was found between PFAS and lower LMI in obese people.

4. Discussion

This population-based study using data from NHANES aimed to investigate the relationship between serum concentrations of PFAS and lean body mass in adolescents and adults. The study findings showed that individuals with high serum concentrations of PFAS generally had lower lean mass in their whole body, trunk, and limbs. Moreover, when analyzing the data by sex, the study found a strong inverse correlation between fractional PFAS and lean body mass in females during both adolescence and adulthood, while males showed minimal association. Additionally, the study observed that obese adults were more likely to have a negative correlation between PFAS and lean body mass, although this association tended to be less pronounced in the normal weight group.

To date, a small number of epidemiological researches [16,17,21,31,32] have confirmed the association between lean body mass and PFAS. Lind [17] used POEM data to explore the relationship between PFAS and both body fat and lean body mass in a middle-aged population. They found a negative correlation between overall lean mass and serum PFHxS levels, but only among males. Another study from the Project Viva cohort [16] presented similar findings, showing that children with higher concentrations of PFOA, PFOS, PFDeA, and PFHxS had reduced lean body mass. A recent prospective study [21] in the United States found that PFNA affects lean body mass and thus bone health, suggesting a direct impact of PFNA on lean body mass. Collectivel, these studies highlight the negative effects of PFAS on lean body mass, which aligns with our findings. However, a cross-sectional study [18] involving 1067 adolescents aged 12–18 years presented a contradictory conclusion, revealing that higher PFHxS exposure was associated with lower body fat mass and higher lean body mass. Although our study also showed some positive correlations for PFHxS in the adolescent group, no such correlations were observed in the subsequent adult groups, suggesting potentially different responses to PFAS exposure across different age groups. Furthermore, it is worth noting that another cross-sectional study did not observe any correlation between PFOS, PFOA, PFNA, PFDeA and lean body mass [17]. This absence of association may be attributed to the limited sample size, population variations, the inadequate consideration of other potential confounding factors (such as diet and exercise patterns), and the varying half-lives and synergistic effect of different PFAS on health. Therefore, our study conducted a subgroup analysis of adolescents and adults to explore the impact of PFAS on people of different ages, sexes and obesity levels in more details. Our research aims to provide a comprehensive comparison of the physiological responses exhibited by distinct populations to PFAS exposure.

Given the sex dependence of PFAS exposure and elimination in the body [33,34], there is a potential impact on sex hormone levels. Our analysis of sex subgroups revealed that PFAS has a more pronounced harmful effect on female groups, particularly adults. Specifically, we observed a significant decrease in whole lean body mass associated with PFDeA ($\beta = -0.220$, 95 % CI: −0.411 to −0.029), PFOS ($\beta = -0.259$, 95 % CI: −0.417 to −0.102) and total PFAS ($\beta = -0.294$, 95 % CI: −0.495 to −0.094), which aligns with findings from prior studies [35–37]. Therefore, our results underscore the importance of implementing additional protective measures to reduce PFAS exposure, especially in women. It is worth noting that PFAS are considered to have “obesogenic” properties and exposure to PFAS may cause changes in the lipid profile of human cells, ultimately affecting the biological processes of fat cells [38,39]. Additionally, studies have shown that PFAS may induce lipid metabolism disorders and oxidative stress [40,41], thereby increasing the risk of obesity. Metabolic disorders and hormonal abnormalities resulting from obesity have detrimental effects on lean body mass [42]. Although there is limited existing research on the impact of obesity on lean mass, and our analysis showed that obese adults exposed to PFAS have lower lean body mass compared to normal-weight adults, especially in the lower limbs, trunk, and whole body. A similar trend was observed among adolescent obesity groups. Hence, it is important to evaluate the risks associated with varying levels of obesity. Finally, significant differences exist in the effects of PFAS on the hormone and metabolic systems of adolescents and adults [43,44]. In adolescents, PFAS may disrupt the dynamic balance of sex and growth hormones, interfering with reproductive development and altering body composition [45]. Conversely, in adults, PFAS may directly interfere [46,47] with sex hormones and thyroid hormones [48], thereby affecting metabolism, fat, and energy balance. Therefore, further research is required to investigate how PFAS interact with age, gender, and obesity in different populations.

It has been illustrated that the binding affinity of PFAS [49–51] varies by their functional groups and carbon-chain length. Our study highlights the significant impact of PFOA, PFDeA, and PFOS onlean body mass. PFOA and PFDeA fall into the category of protracted perfluorinated carboxylic acids, while PFOS belongs to perfluorinated sulfonic acids. Hence, further investigation is necessary to elucidate the effects of different PFAS characteristics on lean body mass loss. Additionally, establishing precise recommended thresholds for various PFAS is critical for effective protection of public health and promotion of environmental sustainability.

Finally, sensitivity analyses revealed that serum albumin and albuminuria had minimal impact on our results, especially in women and obese groups. These findings further strengthen the evidence for a negative association between PFAS and LMI. However, further in-depth studies and exploration of possible mechanistic associations are necessary.

Our study provides evidence supporting an association between certain PFAS and lean body mass loss. This relationship may be attributed to a physiological link between low lean body mass and high blood concentrations of PFAS. Firstly, previous studies have proven that PFOA affects glucose and lipid metabolism through inhibiting AMPK, activating mTOR, increasing P70S6K increase, and upregulating FASN and ACACA (key enzyme for de novo fatty acid synthesis) [52,53], thereby affecting muscle energy production and supply. Recent studies have also demonstrated that exposure to PFAS leads to increased expression of peroxisome proliferator-activated receptor-α (PPARα) [54] in skeletal muscle, disrupting signaling and subsequently affecting muscle mass. Secondly, sex is an important factor in determining the toxic effects of environmental pollutants [55]. Some studies have found that PFAS can competitively bind to the estradiol receptor (ER), thereby affecting the transcriptional activity of the ER. PFOS and PFOA, in particular, can activate the ER and upregulate the expression of ERα [56–59], leading to changes in estrogen and progesterone levels or inhibiting hormone activity [60]. This, in turn, results in reduced lean body mass and alterations in metabolic function [61],

specifically in women. Additionally, PFAS may interfere with the androgen or estrogen pathways by affecting the expression of genes involved in steroid hormone metabolism, such as those related to the growth hormone-insulin-like growth factor (GH-IGF) axis and the steroid hormone axis [62,63]. Thirdly, obesity serves as an important indicator [64] for examining environmental toxicity. PFAS can interfere with hormones such as sex hormone [65,66], testosterone and thyroid hormone [67–69]which are typically expressed at lower levels in obese individuals. Furthermore, PFAS exacerbates metabolic disturbances and reduces muscle mass by worsening insulin resistance [70], increasing insulin secretion and impairing leptin receptor sensitivity [71,72]. In addition, studies showed that PFAS has also been found to contribute to obesity through inflammation [73–75]. Obesity, in turn, leads to increased immune cell infiltration and pro-inflammatory activation in adipose tissue surrounding muscle cells [76]. This results in an increase in pro-inflammatory markers and a decrease in anti-inflammatory markers [77–80]. Whereas more research is urgently needed to fully understand the molecular mechanism and potential toxicological effects of PFAS on human lean body mass.

Nonetheless, our study has several limitations that need to be considered. Firstly, given the cross-sectional design of this study, causal inferences cannot be established. Secondly, the data of PFAS only represents a subsample of 1/3 and the narrow range and limited specimens of PFUA and PFHxS may introduce bias and potentially promote specific results. To ensure accuracy, future studies should include larger sample populations for verification. Additionally, despite adjusting for potential confounding variables, the complexity, volatility of muscle accumulation, as well as individual variations hampered a thorough investigation of the underlying biological mechanisms, such as human albumin levels, glomerular filtration, and other unmeasured biases. Thus, future studies should strive for more comprehensive mechanistic research. Lastly, it is essential to note that stratifying research into adolescents versus adults may introduce heterogeneity, requiring careful interpretation and extrapolation of previous findings. Notwithstanding these limitations, our study used a nationally representative and sufficiently large sample to enhance the plausibility and validity of the extrapolation of the results.

5. Conclusions

Exposure to certain PFAS may be related to adverse health effects on body composition. We detected a significant negative relationship between serum PFAS concentrations and lean body mass, with this correlation being more prominent in women and individuals who are obese. These findings align with the results obtained from the WQS model, indicating that reducing PFAS levels may help mitigate their potential impacts on human health.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because all of our data were derived from published public databases.

Data availability statement

Data comes from the public database NHANES and will be made available on request.

CRediT authorship contribution statement

Xue Jia: Writing – original draft, Methodology, Formal analysis, Data curation. **Wenhui Liu:** Visualization, Validation, Software. **Xiaomeng Ling:** Resources, Project administration. **Juan Li:** Validation, Supervision. **Jing Ji:** Validation, Supervision. **Baozhen Wang:** Writing – review & editing, Project administration. **Min Zhao:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Min Zhao reports financial support was provided by National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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