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RESEARCH ARTICLE

Association of Perfluoroalkyl Substance with Lung Function in the US Population

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ABSTRACT

Background/Aim: Perfluoroalkyl substances (PFASs) are chemical compounds used in consumer products and are linked with increases in cholesterol, thyroid disease, and pregnancy-induced hypertension. However, their association with lung function is not completely understood.

Methods: Cross-sectional 2011-2012 US population data from the National Health and Nutrition Examination Survey (NHANES) were analyzed (n = 1450, aged 12 to 79 years, 50.5% females). Serum concentrations of 4 PFASs, perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS), were assessed using mass spectrometry and categorized into quartiles. Lung function was measured by spirometry as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and the ratio of FEV1/FVC (%). Survey weighted sex stratified adjusted linear regression analysis was used to predict lung function with PFASs quartiles.

Results: In males, compared to females, all 4 PFASs serum concentrations and lung function indices were higher, except FEV1/FVC (%) which was lower than females. No association of any PFAS with decrease in lung function was seen in multivariable-adjusted models in both males and females.

Conclusion: In this exploratory analysis, PFAS exposure was not associated with lung function. PFAS contamination has been ongoing for many years across the US and Ohio, and cleanup efforts are now underway. The association between PFAS exposure and lung function needs further exploration in longitudinal studies.

Keywords: Perfluoroalkyl substances, PFAS, NHANES, Lung function

INTRODUCTION

There are many environmental risk factors that can affect lung function. Common lung conditions such as chronic obstructive pulmonary disease (COPD) and asthma have become more prominent in the United States (US) and Ohio.[1] The prevalence of COPD within the adult population of the US is 6.3% whereas adults in Ohio have a higher COPD prevalence (7.2%).[2] Characterized by a limitation of airflow in the lungs,[3] COPD is more prevalent in males than females, mainly due to the higher smoking rate among males.[4] However, females develop COPD earlier than males due to the smaller lung capacity, leading to faster decline in lung function.[4] Conversely, asthma is more prevalent among females than males in the general population,[3,4] although the prevalence and severity changes with age.[3,4] Prevalence of asthma among adults in the US is 7.9%[5] and among Ohio adults is 9.9%.[6]

Chemical exposures are a relevant public health concern due to the vast amount of chemicals in the environment. Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a group of chemicals that can be found in carpets, clothing, food packaging, firefighting foam, and nonstick cookware coatings.[7,8] Perfluoroalkyl substances have a high chemical and thermal stability[9] which makes them less likely to break down over time. This stability allows industries to use PFASs in many consumer products. Once absorbed through inhalation, oral, or dermal routes, PFASs can accumulate in multiple tissues in humans, including the lungs.[10] Perfluoroalkyl substances have been associated with increased serum cholesterol levels, increased risk of thyroid disease, decreased fertility, and pregnancy-induced hypertension in humans.[9,11]

The lungs are one of the main tissues that accumulate PFASs after exposure.[10] In a study conducted by Timmermann[12] on PFASs exposure and asthma in children, it was noted that children with higher serum PFASs had lower vaccine antibody response to measles, mumps, and rubella (MMR) vaccination. Another recent study in children noted significant association between PFASs exposure and impaired lung function.[13]

There has been scant research on the association between exposures to PFASs and lung function among adults; most of the research has been on animal models or among asthmatic children.[13-15] Given

the limited amount of evidence found in the animal models and conflicting evidence in children in human population, it is important to explore the potential impact of PFASs on lung function among adults.

Perfluoroalkyl substances are endocrine disruptors (ED), and ED can impact males and females differently.[16] Several published studies report sex dependent PFASs impacts such as thyroid function[17] and serum cholesterol.[18] The objective of this exploratory research was to determine the association between PFASs exposure and lung function among the US population. Using the National Health and Nutrition Examination Survey (NHANES) 2011-2012, we tested the hypothesis that increasing serum levels of PFASs, specifically perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS), in the US population will be associated with decreased lung function, and will differ by sex.

METHODS

Setting and Design

This was a cross-sectional study to evaluate the association between PFASs and lung function measured by spirometry (FEV1, FVC, and FEV1/FVC). We used NHANES 2011-2012 data, a population-based survey conducted on individuals within the US.

Participants

The total number of individuals who were interviewed in the 2011-2012 NHANES was 9756, and 9338 of those individuals completed the medical exam. Participants were excluded if they did not have serum PFAS or lung function data. The final sample was comprised of 1450 individuals aged 12 to 79 years.

Procedures

In addition to a household survey that collects data on a variety of risk factors, NHANES conducts clinical assessments in a mobile examination center (MEC).[19] The MEC is used to ensure a standardized examination environment for laboratory measurements, physical assessments, and examinations. All survey materials, consent documents and examination information for the NHANES 2011-2012 data set are publicly available on the NHANES website as part of the Centers for Disease Control and Prevention (CDC).[20]

Measures

Perfluoroalkyl substances biomonitoring was completed on blood samples collected in the MEC. At least 0.5 mL of serum from the blood samples was collected and refrigerated. To test the serum, online solid phase extraction-high performance liquid chromatography-turbo ion spray-tandem mass spectrometry was used to quantitatively detect PFOA, PFOS, PFNA and PFHxS.[20] The lower limit of detection (LLOD) of each PFAS substance is stated as: PFOA (0.10 ng/mL), PFOS (0.20 ng/mL), PFNA (0.08 ng/mL), and PFHxS (0.10 ng/mL).[21] If a sample had results below the LLOD, the NHANES study designers placed an imputed value in the data. This value is calculated by taking the LLOD divided by $\sqrt{2}$ which can be calculated for each PFAS substance: PFOA (0.07 ng/mL), PFOS (0.14 ng/mL), PFNA (0.06 ng/mL), and PFHxS (0.07 ng/mL).

The spirometry measurements were performed in the MEC. The MEC used the Ohio 822/827 dry-rolling seal volume spirometer. Before each spirometry test, a calibration syringe was used to calibrate the spirometer. Individuals were asked a series of safety questions and if the questions were answered with an answer of "Yes," "Refused," or "Don't Know," then the individual did not perform a spirometry test.[20] Spirometry was performed while a participant was standing up, with extended neck and elevated chin. The NHANES examiner had the individual take the deepest breath possible so that the lungs would fill with the maximum amount of air and then blow the air out as fast and forcibly as possible. Forced vital capacity (FVC), the maximum volume of air exhaled forcefully after a maximal inspiration, was calculated. Among individuals aged 11 to 79 years, the forced exhalation has a minimum of 6 seconds of exhalation.[21] Forced expiratory volume in 1 second (FEV1), the volume of air exhaled during the first second, was calculated.[21]

Statistical Analysis

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All tests were exploratory, 2-sided, and conducted at $\alpha = .05$ level of significance. Data were analyzed using survey weights overall and separately by sex. The survey design variables were also included in the analyses to adjust for standard errors due to the complex survey design and to present nationally representative estimates. Descriptive statistics computed for continuous variables (age, PFNA, PFOA, PFOS, PFHxS, FEV1, FVC and FEV1/FVC) included measures of centrality (mean, median) and dispersion (standard error, interquartile range). Frequency distributions were examined for categorical variables (race/ethnicity and annual household income). Race/ethnicity was recoded into 3 values: non-Hispanic white (reference), non-Hispanic black, and all others. Annual household income was recoded into 3 values: <$25000 (reference), $25000 to <$55000, and ≥$55000.

Rao-Scott chi-square tests were used to determine the statistical significance between the categorical variables across sex. The statistical significance of associations between the continuous variables across sex was tested using Proc Surveyreg for normally distributed variables (age, FEV1, FVC, and FEV1/FVC) or by the Mood's Median test (svyranktest procedure in R) for nonnormally distributed continuous variables (PFNA, PFOA, PFOS, and PFHxS).

As PFASs were not normally distributed, each individual PFAS was categorized into quartiles. Four individual PFASs (exposures/predictor) were tested in each of the lung function test (outcome/dependent) analyses (FVC, FEV1, and FEV1/FVC).

Survey weighted linear regression analysis was performed to assess association between each PFAS categorical variable separately as a predictor (PFNA, PFOA, PFOS, and PFHxS) and the outcome variable (FEV1, FVC, or FEV1/FVC). First, unadjusted linear mod-

els were analyzed, followed by age-adjusted linear regression, and then multivariable regression for other covariates including age, annual household income, race/ethnicity. A total of 12 unadjusted linear regressions, 12 age-adjusted linear regressions, and 12 multivariable linear regressions were analyzed. Categorical variables with more than 2 levels were dummy coded including PFAS quartiles, annual household income, and race/ethnicity. The assumptions for each of the regression models were checked. Although the study was exploratory in nature, a Bonferroni correction was applied due to the number of tests to protect from type 1 error. The new *P* value was the alpha value (α original = 0.05) divided by the number of comparisons (36): (α altered = 0.05/36) = .001. To determine if any of the 36 models was statistically significant, the *P* value must be less than 0.001.

RESULTS

Table 1 summarizes information for study participants overall and by sex. Among the overall weighted sample of 1450 NHANES participants, 50.5% were female. The mean age of individuals was 40.9 ± 0.8 years. A higher proportion of this group had annual household income ≥$55000. Compared to non-Hispanic black and other races, non-Hispanic white constituted the prevalent group at 67% overall and when comparing males versus females. No significant differences between sexes were noted for age, annual household income and race/ethnicity.

Male participants had a higher median serum concentration for all 4 PFASs (0.9, 2.4, 8.5, 1.8 vs 0.8, 1.8, 5.2, 0.9, $P = 0.001$, $P = 0.004$, $P < 0.0001$ and $P < 0.0001$) respectively, compared to females. Males also had higher lung function, FEV1 (3758.6 vs 2737.5; $P < 0.0001$) and FVC (4815.7 vs 3425.1; $P < 0.001$) compared to females. However, the reverse was seen in the ratio of FEV1/FVC in which female had the highest spirometry measure (79.9 vs 78.0; $P = 0.002$) compared to males, respectively.

In survey weighted and multivariable linear regression analysis presented in **Tables 2, 3, and 4** none of the 4 PFASs exposures were associated with any of the 3 lung function tests in males or females at Bonferroni corrected alpha level (0.05/36) = $P < 0.001$.

Tables S1, S2, and S3 (see Supplemental Materials) provide unadjusted, age-adjusted, and multivariable-adjusted regression results; no significant association between PFASs exposure and lung function was seen at Bonferroni corrected alpha level (0.05/36) = $P < 0.001$.

Table 1. Weighted Characteristics of 2011-2012 NHANES Participants, Overall and by Sex

Characteristic	Overall (N = 61244861)	Male (49.5%)	Female (50.5%)	*P* value*
Age (years), *mean (se)*	40.9 (0.8)	40.5 (1.0)	41.3 (1.0)	0.55
Household income, % (*se*)				0.55
<$25000	19.6 (2.5)	18.6 (2.8)	20.6 (2.9)	
$25000-$54999	29.8 (2.4)	29.1 (2.7)	30.6 (3.1)	
≥$55000	50.6 (3.4)	52.3 (3.5)	48.8 (3.7)	
Race/Ethnicity, % (*se*)				0.32
Non-Hispanic white	67.0 (3.8)	65.9 (3.6)	68.1 (4.4)	
Non-Hispanic black	11.1 (2.4)	10.9 (2.2)	11.3 (2.7)	
All Other	21.9 (2.6)	23.3 (3.6)	20.6 (2.7)	
PFAS (ug/L), *median (IQR)*				
PFNA	0.9 (0.6, 1.3)	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	0.001†
PFOA	2.1 (1.5, 3.1)	2.5 (1.8, 3.4)	1.8 (1.3, 2.7)	<.001†
PFOS	6.6 (4.2, 10.4)	8.5 (5.5, 12.8)	5.2 (3.2, 7.9)	<.0001†
PFHxS	1.3 (0.8, 2.3)	1.8 (1.1, 2.9)	1.0 (0.6, 1.7)	<.0001†
Lung function tests, *mean (se)*				
FEV1 (mL)	3243.3 (25.6)	3758.6 (43.7)	2737.5 (25.9)	<.0001
FVC (mL)	4113.9 (34.9)	4815.7 (62.4)	3425.1 (34.7)	<.0001
FEV1/FVC (%)	79.0 (0.3)	78.0 (0.5)	79.9 (0.4)	0.002

*P values reported from Rao-Scott chi-square test for categorical variables and Proc Surveyreg for continuous variables comparing males to females
†P values reported from the Mood's Median test for nonnormally distributed continuous variables

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Table 2. Association of PFASs Serum Concentration with FEV1 in NHANES 2011-2012 Participants in Multivariable Survey Weight Adjusted Linear Regression

	Male			Female		
	B (95% CI)	f-value	*P*	B (95% CI)	f-value	*P*
PFOA	Referent	2.43	0.10	Referent	1.14	0.36
2nd	89.62 (-177.18, 356.42)			-66.16 (-232.69, 100.37)		
3rd	14.90 (-221.68, 251.47)			18.37 (-128.28, 165.02)		
4th	170.13 (-60.48, 400.73)			12.59 (-142.57, 167.75)		
PFOS	Referent	4.14	0.02	Referent	1.04	0.40
2nd	356.25 (120.62, 591.88)			26.87 (-126.13, 179.88)		
3rd	355.75 (99.69, 611.80)			32.63 (-133.7, 198.99)		
4th	303.90 (89.92, 517.89)			132.49 (-27.29, 292.28)		
PFNA	Referent	0.25	0.86	Referent	1.15	0.36
2nd	-69.01 (-240.62, 102.60)			-25.62 (-204.14, 152.90)		
3rd	-26.81 (-227.21, 173.59)			74.73 (-97.75, 247.22)		
4th	12.07 (-193.83, 219.97)			47.91 (-131.26, 227.07)		
PFHxS	Referent	1.68	0.21	Referent	1.91	0.17
2nd	29.11 (-258.25, 316.49)			118.54 (-19.45, 256.52)		
3rd	167.37 (-104.11, 438.85)			29.4 (-114.20, 173.06)		
4th	215.99 (-50.01, 482.01)			31.02 (-146.78, 208.82)		

*In all models, the reference category was the respective first PFAS quartile.
Variables that were adjusted for: age, annual household income and race/ethnicity
Note: Degrees of freedom for each f-value is 3
Bonferroni corrected adjusted alpha was .001 (.05/36).

Table 3. Association of PFASs Serum Concentration with FVC in NHANES 2011-2012 Participants in Multivariable Survey Weight Adjusted Linear Regression

	Male			Female		
	B (95% CI)	f-value	*P*	B (95% CI)	f-value	*P*
PFOA	Referent	1.62	0.22	Referent	0.15	0.93
2nd	116.06 (-170.20, 402.32)			-41.72 (-230.72, 147.27)		
3rd	-4.39 (-270.07, 261.28)			-51.87 (-233.32, 129.58)		
4th	164.60 (-128.41, 457.61)			-8.36 (-214.27, 197.54)		
PFOS	Referent	3.13	0.05	Referent	0.06	0.98
2nd	412.95 (103.30, 722.60)			15.17 (-185.23, 215.57)		
3rd	381.33 (85.26, 677.40)			16.29 (-175.35, 207.94)		
4th	311.99 (15.47, 608.53)			43.93 (-177.57, 265.42)		
PFNA	Referent	0.19	0.90	Referent	0.54	0.66
2nd	-62.61 (-247.17, 121.96)			-46.40 (-284.68, 191.89)		
3rd	-27.76 (-289.88, 234.36)			73.08 (-197.81, 343.97)		
4th	-7.57 (-219.71, 204.57)			-21.50 (-263.17, 220.13)		
PFHxS	Referent	1.15	0.36	Referent	3.01	0.06
2nd	45.02 (-306.17, 396.21)			188.51 (7.60, 369.42)		
3rd	170.75 (-138.62, 480.12)			87.18 (-128.04, 302.40		
4th	231.36 (-68.31, 531.02)			20.40 (-226.05, 266.85)		

*In all models, the reference category was the respective first PFAS quartile.
Variables that were adjusted for: age, annual household income and race/ethnicity
Note: Degrees of freedom for each f-value is 3
Bonferroni corrected adjusted alpha was .001 (.05/36).

Table 4. Association of PFASs Serum Concentration with FEV1/FVC in NHANES 2011-2012 Participants in Multivariable Survey Weight Adjusted Linear Regression

	Male			Female		
	B (95% CI)	**f-value**	***P***	**B (95% CI)**	**f-value**	***P***
PFOA	Referent	0.43	0.74	Referent	3.24	0.05
2nd	-0.09 (-2.63, 2.46)			-0.99 (-2.76, 0.77)		
3rd	0.70 (-1.92, 3.33)			1.65 (0.20, 3.10)		
4th	0.98 (-1.16, 3.11)			0.43 (-1.65, 2.52)		
PFOS	Referent	2.23	0.12	Referent	6.51	0.004
2nd	0.59 (-1.25, 2.44)			0.57 (-0.91, 2.05)		
3rd	1.22 (-0.12, 2.56)			0.41 (-1.61, 2.43)		
4th	1.06 (-1.01, 3.13)			3.01 (1.50, 4.51)		
PFNA	Referent	0.26	0.85	Referent	3.33	0.04
2nd	-0.33 (-2.17, 1.52)			0.41 (-0.82, 1.63)		
3rd	0.08 (-2.06, 2.23)			0.21 (-1.39, 1.82)		
4th	0.71 (-1.24, 2.67)			2.05 (0.46, 3.64)		
PFHxS	Referent	0.28	0.84	Referent	1.36	0.29
2nd	-0.24 (-2.03, 1.55)			-0.66 (-1.99, 0.68)		
3rd	0.59 (-1.33, 2.50)			-1.44 (-3.25, 0.38)		
4th	0.57 (-2.08, 3.22)			0.41 (-1.18, 1.99)		

*In all models, the reference category was the respective first PFAS quartile.
Variables that were adjusted for: age, annual household income and race/ethnicity.
Note: Degrees of freedom for each f-value is 3
Bonferroni corrected adjusted alpha was .001 (.05/36).

DISCUSSION

In this exploratory analysis using data from US adults, we did not observe an association between serum PFASs concentration with lung function. To our knowledge this analysis is one of the very first population studies conducted to assess impact of PFASs on lung function among US adults.

Previous research[22] on the impact of PFASs on lung function is generally limited to children and show mixed results. Similar to our results, a recent study in adolescents, who as children were exposed to the World Trade Center (WTC) disaster dust (living nearby), showed no significant association between serum PFASs and lung function parameters measured by spirometry, plethysmography, and oscillometry, asthma diagnosis, or eosinophil count. As compared to unexposed age matched controls, these adolescents had higher serum PFASs levels due to exposure to WTC-linked dust exposure containing PFASs and other chemicals when they were children. These results underscore the need for more longitudinal studies to explore impact of PFASs on lung function.

Conversely, in other population studies, children diagnosed with asthma had higher mean serum PFAS levels compared to healthy children.[13] In a study conducted among Taiwanese children, serum PFASs were positively associated with decreased lung function and immunological markers among those diagnosed with asthma.[14] Perfluoroalkyl substances were not significantly associated with pulmonary function among healthy children. A previous study using data from adolescents enrolled in NHANES 1999-2000 and 2003-2008 reported a positive relationship between PFOA and self-report of asthma, and wheezing.[15] However, serum PFOS, PFNA, and PFHxS concentrations were unrelated to asthma. Higher serum PFASs concentrations have been associated with increased inflammatory markers,[23] suggesting that PFASs may induce inflammation and predispose people to impaired lung function. In another NHANES analysis in children, no association between lung function and serum PFASs concentrations was noted, although antibody response to routine vaccine was muted, suggesting that PFASs may impair immunological responses in children.[24]

Relatively more studies have been conducted using animal models to explore PFASs exposure and lung function. In a study by Ye,[7] PFAS exposure was linked with neonatal mortality in mice, which was caused by underdeveloped lungs. In a separate study of mice pups, exposure to PFAS altered airway function, induced airway inflammation, and increased the airway response.[4] Perfluoroalkyl substances negatively impact the development of mammals, resulting in lower birth weight and neonatal mortality.[12] Neonatal

mortality in animals was caused by underdeveloped lungs and the failure of lung function.[12] Other outcomes associated with PFAS and lungs include an increase in airway inflammation and altered airway function in animal models.[9]

Chance could be an explanation of our findings; even though our results show somewhat consistent negative associations between different PFASs and lung function. Other possible explanations for this negative association could include bias and residual confounding. We adjusted for known confounders, except smoking. This was due to the complexity of methods utilized to collect smoking data in NHANES 2011-2012. However there could still be unmeasured confounders that bias the observed negative association. One of those unmeasured confounders could be genetic/biological factors that cannot be measured quantitatively.

As this was a cross-sectional study, based on a national survey, selection bias was minimized by utilizing random sampling. To reduce information bias, the data collection team was provided extensive training to reduce errors in data collection, interviews, and data entry.

PUBLIC HEALTH IMPLICATIONS

Perfluoroalkyl substances contamination has been noted all across the country, including Ohio. Of particular concern is PFAS presence in the Ohio drinking water supply given Ohio's industrial legacy. Perfluoroalkyl substances contamination is a public health concern because having a safe drinking water supply is an essential requirement for protecting public health. Several regions in Ohio have a history of PFAS water contamination including the mid-Ohio Valley communities, which were exposed to PFOA release in the water since 1950s from upstream industry in Parkersburg, West Virginia.[23] Other water systems that have been contaminated in Ohio include Cleveland, Cuyahoga County, Greene County, Gallia, Mahoning, and Montgomery County.[24] In the mid-Ohio Valley population, PFOA exposure was associated with a number of diseases including high cholesterol, ulcerative colitis, testicular cancer, kidney cancer, and pregnancy-induced hypertension.[23] With all of the PFAS exposure within Ohio over the years, there could be more negative health impacts which can only be determined through further studies in areas affected by PFAS contamination. Overall, people are concerned about the health impacts of PFAS, which are not clearly understood, and more scientific evidence and epidemiological studies are needed.

Conclusion

This cross-sectional study provides some evidence that current population exposure to PFASs may not adversely impact lung function. The existing evidence of effect of PFASs on lung function in different age groups and among those diagnosed with asthma is inconsistent, and prospective studies are needed.

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