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The Association of Perfluoroalkyl Substance Exposure and Lung Function in the U.S. Population

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Abstract

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

Methods: Cross sectional 2011-12 U.S. population data from the National Health and Nutrition Examination Survey (NHANES) was used (*N*=1,450, aged 12 to 79 years, 52% men). Serum concentration of four PFASs, perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) were assessed using mass spectrometry and were categorized into tertiles. Lung function was measured by spirometry as forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the ratio of FVC/FEV1 (%). Sex stratified adjusted linear regression analysis was used to predict lung function with PFASs tertiles.

Results: In men all four PFASs serum concentrations and lung function was higher, except FVC/FEV1 (%) which was lower than women ($p<.001$ for all). In men, compared with low tertiles, high exposure to PFOS, PFNA, predicted a significant decrease in FEV1 and FVC, respectively, and PFOA, PFOS, and PFHxS predicted significant low FVC/FEV1 (%) in unadjusted models. In women, compared with low tertiles, high exposure to all PFASs predicted a significant decrease in FEV1, FVC and FVC/FEV1 (%) (except PFHxS in FVC), respectively, in unadjusted models ($p<.001$). No association was seen in adjusted models in both men and women.

Conclusion: High PFASs exposure has a consistent significant negative impact on female lung function in unadjusted analysis and this association needs further exploration.

Keywords: Perfluoroalkyl Substances, PFAS, NHANES, Public Health, Lung Function

The Association of Perfluoroalkyl Substance Exposure and Lung Function in the U.S. Population

Chemical exposures are a relevant public health concern due to the vast amount of chemicals in the environment to which the public is exposed, often with unknown side effects. Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a group of chemicals that can be found in carpets, clothing, food packaging, firefighting foam, and non-stick cookware coatings (Pérez et al., 2013; Kirk et al., 2018; Timmermann et al., 2017). These chemicals are widely used in common consumer products due to their hydrophobic, to water repellant, and lipophobic, insoluble in fat, natures (Pérez et al., 2013; Kirk et al., 2018). PFASs have a high chemical and thermal stability (Qin et al., 2017) meaning that they are less likely to break down in normal day-to-day conditions. This stability allows industries to use PFASs in the many consumer products. Once absorbed through inhalation, oral or dermal routes, PFASs have been found to accumulate in multiple tissues in humans, including the lungs (Pérez et al., 2013). PFASs have also been found to cause an increase in cholesterol, increase the risk of a thyroid disease, decreased fertility and pregnancy-induced hypertension in humans (Agency for Toxic Substances and Disease Registry [ATSDR], 2018a; ATSDR, 2018b).

The lungs are one of the main tissues that accumulate PFASs after exposure (Pérez et al., 2013) and yet little research has been done regarding lung function and outcomes with PFAS exposure. There has been scant research on the association between exposures to PFASs and lung function in the human population; most of the research has been on animal populations. In a study conducted by Timmermann et al. (2017), PFASs exposure and asthma in children were found to have a lower vaccine antibody response to measles, mumps and rubella (MMR) vaccination. Children with an increased serum concentration of PFAS had higher odds of history

of asthma in unvaccinated children compared to those who were vaccinated. A study on the exposure of PFASs and children found that there is an association between PFASs and impaired lung function (Qin et al., 2017).

More research has been conducted on animals involving PFASs and lung functions. Studies have found that PFASs negatively impact the development of mammals, resulting in lower birth weight and neonatal mortality. Research has demonstrated that the neonatal mortality in animals was caused by under-developed lungs and the failure of lung function (Ye et al., 2012). Other outcomes associated with PFAS and lungs include an increase in the immunoglobulin IgE, which is associated with allergy response (Qin et al., 2017; Timmermann et al., 2017) and an increase in airway inflammation and altered airway function in animal models (Qin et al., 2017). Given the limited amount of evidence found in the animal models involving the negative impact of PFASs on lung function, it is important to explore if the same is true in human population.

The burdens of lung function disease, such as chronic obstructive pulmonary disease (COPD), and asthma, have become more prominent in the United States (U.S.) (Cukic, Lovre, Dragisic, & Ustamujic, 2012). COPD is characterized by the limitation of airflow in the lungs (Carey et al., 2007). COPD is more prevalent in males than females, mainly due to the smoking rate in males being higher than in females (Carey et al., 2007; LoMauro & Aliverti, 2018). However, females develop COPD earlier than males due to the smaller lung capacity, creating a faster decline in lung function (LoMauro & Aliverti, 2018). Asthma is more prevalent among females than males in the general population (Carey et al., 2007; LoMauro & Aliverti, 2018), although the prevalence and severity changes with age (Carey et al., 2007). Likewise, in children, asthma incidence is more frequent in males (LoMauro & Aliverti, 2018).

Statement of Purpose

The objective of this project is to determine what types of association PFASs exposure have with lung function among the U.S. population. Using the National Health and Nutrition Examination Survey (NHANES) 2011 to 2012, we hypothesized that increasing serum levels of PFASs, specifically perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS), in the U.S. population would be associated with decreased lung function, as assessed by spirometry, and will differ by gender.

Literature Review

Perfluoroalkyl and Polyfluoroalkyl Substances

PFASs are a group of chemicals that consist of hundreds of different types, but only about twelve are commonly found and studied (Rodriguez-Jorquera & Toor, 2015; ATSDR, 2018b). PFASs are chemicals that have a high thermal and chemical stability (Qin et al., 2017). PFASs are made up of a carbon backbone, which can vary from a length of four carbons to twelve carbons, with fluorine substitutions (ATSDR, 2018c) (see Figure 1). These carbon-fluorine bonds provide strength giving the thermal and chemical stability that allows the chemicals to be resistant to break down (Pérez et al., 2013). PFASs have a ‘head’ and a ‘tail’ (Figure 1). The ‘head’ and ‘tail’ can vary based on which PFAS chemical is being examined, due to different molecular structures which affects the charge of the ‘head’. In a review published by Kirk and colleagues (2018), the ‘head’ of the PFAS molecule was found to regulate where in the body that the PFAS would accumulate.

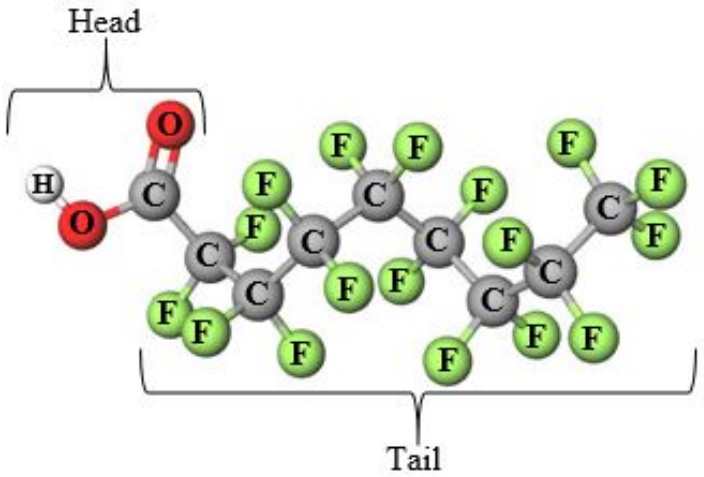

Figure 1. PFNA molecule structure. Made using MolView (Bergwerf, 2015).

PFASs also have a hydrophobic and lipophobic nature (Pérez et al., 2013; Kirk et al., 2018). Hydrophobic is a term used when referring to substances that are able to repel water, and lipophobic is a term used when referring to substances that are not soluble in lipids or non-polar solvents, such as fats. Due to these properties, PFASs are widely used in manufacturing products.

PFASs bind to serum proteins with high affinity. PFASs especially bind to albumin, which acts as a transporter of insoluble molecules, because of the high affinity between the receptor and its ligand (Kirk et al., 2018). PFASs bioaccumulate in the body, meaning that they become concentrated inside the body due to the fact that the rate at which the body absorbs PFASs is faster than what the body can excrete or catabolize. Perfluoroalkyl substances are excreted mostly through the renal system (ATSDR, 2018b; Pérez et al., 2013). A study by Pérez et al. (2013), found that PFASs have the highest accumulation in lung tissues. Liver and brain tissue were also found to accumulate PFASs.

Exposures to PFASs

There are many ways that humans can be exposed to PFAS. Some of the products that contain PFASs include food packaging, firefighting foam, non-stick cookware, photographic films and furniture (Pérez et al., 2013; Kirk et al., 2018; Timmermann et al., 2017). There are

three exposure routes into the body; the oral route into the body is the most rapid and the most common form of exposure for the general population. The dermal route is possible but less likely; however, it could be an exposure route for those occupational workers who handle products with PFAS (Rodriguez-Jorquera & Toor, 2015; ATSDR, 2018b). The inhalation route has not been studied enough in epidemiological studies, but is considered the most common form of exposure route for the occupational workers (Rodriguez-Jorquera & Toor, 2015; ATSDR, 2018b).

PFAS exposure could also occur through contaminated water, soil, air, and food. The industries that manufacture products release PFASs into the surrounding air or the surface water around the industrial plant (ATSDR, 2018b; ATSDR, 2018c). Manufacturing of some PFAS products in the U.S. has been phased out since the early 2000's (ATSDR, 2018c). PFAS still remain present in the environment due to their resistance to break down. Thus, they seep into the ground-water, and they persist in the soil. Wind and rain are able to carry the chemicals great distances, spreading the exposure radius to places where there are no manufacturing plants (ATSDR, 2018a; ATSDR, 2018b).

Health Effects

Several health effects have been associated with PFAS exposures. The main health effects associated with humans are increased cholesterol, an increased risk of thyroid disease and a decrease in female fertility (ATSDR, 2018a; ATSDR, 2018b). Pregnant woman are also affected by PFAS exposure; they have an increased chance of high blood pressure, pre-eclampsia and lower birth weight in infants (ASTDR, 2018a).

Animal studies have been conducted to help determine the health effects caused by PFASs exposure. Some of the main health effects found in animal studies have been liver

damage, immune toxicity, and cancer of the liver, pancreas and reproductive organs (ASTDR, 2018b; Rodriguez-Jorquera & Toor, 2015). Animal studies on PFASs have also been found to impact birth outcomes, such as delayed development, increased birth defects, reduced birth weight and a reduced number of live births (ATSDR, 2018a; Rodriguez-Jorquera & Toor, 2015).

Respiratory health effects. Few studies have been conducted on the respiratory effects of PFASs on humans. There are, however, a few studies that demonstrate that PFASs have some impact on the respiratory system. In a study conducted by Timmermann et al. (2017), PFASs exposure and asthma in children were found to have a lower vaccine antibody response to the MMR vaccination. Children with an increased serum concentration of PFAS had higher odds of history of asthma in unvaccinated children compared to those who were vaccinated. Another study conducted by Qin et al. (2017) found an association between PFAS exposure and impaired lung function in children. The lungs are one of the main tissues in which PFASs accumulate (Pérez et al., 2013).

More studies have been done on animals to test the respiratory effects caused by PFASs. In a study by Ye et al. (2012), PFAS exposure caused neonatal mortality in mice, which was caused by under-developed lungs. Animals exposed to PFAS have also been found to increase serum immunoglobulin E (Qin et al., 2017; Timmermann et al., 2017). In a study conducted with mice pups, exposure to PFAS were found to cause altered airway function, induced airway inflammation and increased the airway response in an allergic murine model (Qin et al., 2017).

Spirometry

Spirometry is a pulmonary function test, also known as a breathing test, which is able to analyze overall lung function (Sood, Dawson, Henkle, Hopkins-Price, & Quails, 2007). Spirometry is used in testing and surveillance for lung diseases, such as asthma, COPD, chronic

bronchitis, emphysema and pulmonary fibrosis (Sood et al., 2007; Coates et al., 2013). The test is conducted by measuring the volume of air exhaled by the patient. The volume can either be calculated directly, when the patient has exhaled into an expandable chamber, or by measuring the air flow and then calculating the volume from the air flow (Coates et al., 2013). Spirometry tests are conducted multiple times in one sitting to ensure consistent results. The common spirometry measurements include forced vital capacity (FVC), forced expiratory volume (FEV) and forced vital capacity divided by forced expiratory volume (FEV/FVC).

FVC is the largest amount of air that a patient is able to forcibly exhale after breathing in as deep as they can, it is done to calculate the magnitude of restricted breathing (Coates et al., 2013; Hankinson et al., 2010). The lower the FVC the greater the breathing restriction. Forced expiratory volume in one second (FEV1) is used to calculate how much air a patient can force from their lungs in one second (Coates et al., 2013; Hankinson et al., 2010). FEV1 calculations help determine the severity of breathing problems; see Table 1. A ratio of FEV1 to FVC is calculated to determine if the results are normal when compared to reference values (Coates et al., 2013). Reference values set for each of these variables based on NHANES III, see Table 1 (Sood et al., 2007; Hankinson et al., 2010).

Table 1

NHANES III Reference Values of Spirometry (FEV1 and FEV1/FVC)

Degree of Severity	**FEV1 % Predicted**	**FEV1/FVC Ratio**
Normal	~100	.70-.80
Mild	>70	<.70
Moderate	60-69	<.70
Moderately Severe	50-59	<.70
Severe	35-49	<.70
Very Severe	<35	<.70

Methods

Data Source and Study Sample

This was a cross sectional study using existing data from NHANES 2011 to 2012 from healthy individuals (N = 1,450; 12 years through 79 years old; 752 men and 698 women) to evaluate the association between PFASs and lung function measured by spirometry (FEV1, FVC, and FEV1/FVC). NHANES is a population-based survey conducted on individuals within the U.S. population in assigned subgroups focusing on specific diseases and risk factors. The total number of individuals who were interviewed in the 2011 to 2012 NHANES was 9,756 and 9,338 of those individuals were examined (Centers for Disease Control and Prevention, National Center for Health Statistics [CDC NCHS], 2018). These participants are examined in a mobile examination center (MEC).

The MEC is used to ensure a standardized examination environment for laboratory measurements, physical assessments and examinations. Questionnaires were also used to collect demographic and personal information (age, sex, race/ethnicity, income, education, and occupation), medical history (current health status and chronic conditions), physical activity, alcohol and tobacco use or exposure, and reproductive history. Physical examination included measurement of height and weight. The MEC is able to collect biological specimens such as, blood, urine, vaginal swabs and oral rinse. All of the MEC laboratory staff complete training to learn the standardized NHANES laboratory protocols. All survey materials, consent documents and examination information for the NHANES 2011 to 2012 dataset are publicly available on the NHANES website as part of the Centers for Disease Control and Prevention (CDC NCHS, 2018; CDC NCHS, 2015a; CDC NCHS, 2015b).

PFASs Concentration

PFASs chemicals, also known as polyfluoroalkyl chemicals (lately PFCs) in NHANES 2011 to 2012 dataset, were extracted in the blood samples taken in the MEC. The serum from the blood samples, a minimum of 0.5mL, is collected and are refrigerated within four hours of collection. To test the serum, online solid phase extraction-high performance liquid chromatography-turbo ion spray-tandem mass spectrometry (online SPE-HPLC-TIS-MS/MS) was used to quantitatively detect PFOA, PFOS, PFNA and PFHxS (CDC NCHS, 2013). The serum samples are prepared with 0.1M of formic acid, after being thawed and then inserted in the automated SPE-HPLC-TIS-MS/MS. The mass spectrometer is calibrated every three to six months and the instrument sensitivity is checked before each test of samples (CDC NCHS, 2013). 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) (CDC NCHS, 2014a). If a sample had results below the lower limit of detection the NHANES study designers placed an imputed value in the database. This value is calculated by taking the LLOD divided by square root of two (LLOD/$\sqrt{2}$), 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) (CDC NCHS, 2014a; CDC NCHS, 2013).

Spirometry Measurement

The spirometry measurements were done with the individuals in the MEC. The MEC used the Ohio 822/827 dry-rolling seal volume spirometer. Before each test was performed using the spirometer, a calibration syringe was used to calibrate the spirometer. Before each test, the individuals were asked a series of safety questions (see Appendix A), and if the questions were answered positively (“Yes”, “Refused”, or “Don’t Know”) then the individual did not perform a

spirometry test (CDC NCHS, 2011). The spirometry was performed by having the individuals stand up, unless physically incapable, extend their neck and elevate their chin. A nose clip was placed on the nose to prevent any air leaks (CDC NCHS, 2014b). 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. When exhaling into the mouthpiece of the spirometer, the individual made sure as to keep their lips around it to create a tight seal (CDC NCHS, 2014b). FVC, the maximum volume of air exhaled forcefully after a maximal inspiration, was calculated. In an adult (11 to 79 years old), the forced exhalation has a minimum of six seconds of exhalation and in children (six to ten years old), the forced exhalation has a minimum of three seconds of exhalation (CDC NCHS, 2014b; CDC NCHS, 2011). FEV1, the volume of air exhaled during the first second, was calculated (CDC NCHS, 2011).

Statistical Analysis

Analyses were performed using the Statistical Package for the Social Science (SPSS) (IBM SPSS Statistics for Mac, Version 25.0. Armonk, NY: IBM Corp., 2017). All tests were two sided and conducted at the $\alpha = .05$ level of significance. Analysis was presented for the overall data set and also by gender. Descriptive statistics computed for continuous variables included measures of centrality (mean, median) and dispersion (standard deviation, range) (age, PFNA, PFOA, PFOS, PFHxS, FEV1, FVC and FEV1/FVC). Frequency distributions (number and percentage) were examined for categorical variables (race/ethnicity and annual household income). Race/ethnicity was recoded from five values into three values: non-Hispanic White (reference), non-Hispanic Black, and all others. Annual household income was recoded from fourteen values into three values: <$25,000 (reference), $25,000 to <$55,000, and $55,000+ (see Appendix B).

Chi-square test was used to determine the statistical significance between the categorical variables across gender. The statistical significance of associations between the continuous variables across gender was tested by an independent-sample t-test for normally distributed variables (age, FEV1, FVC, and FEV1/FVC) or by a Mann-Whitney U test for non-normally distributed continuous variables (PFNA, PFOA, PFOS, and PFHxS).

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

Linear regression analysis was performed to assess association between each PFAS tertile separately as predictor (PFNA, PFOA, PFOS, and PFHxS) and the outcome variable (FEV1, FVC, or FEV1/FVC). First unadjusted linear models 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 two levels were dummy coded including, PFAS tertiles, annual household income, and ethnicity. Analysis was repeated using continuous log transformed PFASs variables.

Results

Descriptive Statistics

As seen in Table 2, the overall sample of 1,450 NHANES participants, 51.9% were male. The mean age of individuals was 39.26 ± 18.85 years. A higher proportion of this group had annual household income ≥$55,000. Compared to non-Hispanic White and non-Hispanic Black, other races constituted the prevalent group at 39% overall and when comparing males versus

females (Table 2). No significant differences between gender was found for age, annual household income, and race/ethnicity.

Table 2

Characteristics of 2011-2012 NHANES Participants, Overall and by Gender: Male and Female

Characteristic Variable	Overall N= 1450	(51.9%)	(48.1%)	p-value*
Age (years), *mean (SD)*	39.26 (18.85)	39.42 (18.96)	39.09 (18.75)	.737
Annual Household Income, *n*				.644
<$25,000	427 (29.4)	214 (28.5)	213 (30.5)	
$25,000-$54,999	443 (30.6)	230 (30.6)	213 (30.5)	
≥$55,000	580 (40.0)	308 (41.0)	272 (39.0)	
Race/Ethnicity, *n (%)*				.865
NonHispanic White	497 (34.3)	253 (33.6)	244 (35.0)	
NonHispanic Black	386 (26.6)	203 (27.0)	183 (26.2)	
All Other	567 (39.1)	296 (39.4)	271 (38.8)	
PFNA (ug/L), *median (IQR)*	.89 (.74)	.98 (.78)	.81 (.64)	<.001†
PFOA (ug/L), *median (IQR)*	2.05 (1.47)	2.33 (1.40)	1.73 (1.34)	<.001†
PFOS (ug/L), *median (IQR)*	6.33 (6.68)	7.96 (7.27)	4.99 (5.27)	<.001†
PFHxS (ug/L), *median (IQR)*	1.22 (1.41)	1.64 (1.60)	.91 (.98)	<.001†
FEV1 (mL), *mean (SD)*	3101.09 (880.0)	3539.49 (864.59)	2628.77 (611.33)	<.001
FVC (mL), *mean (SD)*	3868.86 (1058.77)	4475.55 (968.90)	3215.23 (702.84)	<.001
FEV1/FVC (%), *mean (SD)*	80.34 (8.71)	78.98 (8.91)	81.81 (8.25)	<.001

*p-values were found by using the chi-square test for categorical variables and a t-test for continuous variables.
†p-values were found by using the mann-whitney U test for non normal distribution of the continuous variables.
p-value reports differences between the two categories: Male and Female.

Male participants had a higher exposure to all four PFASs (0.98, 2.33, 7.96, 1.64 vs 0.81, 1.73, 4.99, 0.91; all $p < .001$) respectively, compared to females. Males also had higher spirometry measures of FEV1 (3539.49 vs 2628.77; $p < .001$) and FVC (4475.55 vs 3215.23; $p < .001$) compared to females. However, the reverse was seen in the ratio of FEV1/FVC in which female had the highest spirometry measure (81.81 vs 78.98; $p = <.001$) compared to males, respectively. In this sample the overall PFNA value was higher than the national value (CDC DHHS, 2019) reported from NHANES 2011 to 2012 (.89 vs .88), as well as PFOS (6.33 vs

6.31). The overall PFOA value was lower than the national value (2.05 vs 2.08) as well as PFHxS (1.22 vs 1.28).

Linear Regression Analysis

In linear regression analysis (Table 3), when compared with low PFOS tertiles, in men, high exposure showed a significant decrease in FEV1 in unadjusted models. In unadjusted models, with PFNA high exposure showed a negative association with FEV1 (trend towards significance, $p = .062$). In women, all four PFAS's high exposure tertiles predicted a decrease in FEV1 in the unadjusted models (Table 3), additionally the same effect was seen for PFNA for medium exposure. However, in neither men nor women, there was no such negative association between PFASs and FEV1 seen in age or multivariable adjusted models. In men, almost all PFASs in general, except PFNA, showed a significant increase in FEV1 in medium and high tertiles, compared to the low tertile, both in the age adjusted and multivariable adjusted models. No such association was seen in unadjusted models in men. In the rest of our descriptions of our results, only the negative associations of all four PFASs with lung function are presented.

Table 3

Association of PFASs Serum Concentration with FEV1 in NHANES 2011-2012 Participants using Unadjusted and Multivariable Adjusted Linear Regression

		FEV1			
		Male		Female	
		B (95% CI)	p-value	B (95% CI)	p-value
PFOA					
Unadjusted	Med	67.23 (-84.25, 218.71)	.384	-33.40 (-144.15, 77.34)	.554
	High	35.66 (-116.28, 187.60)	.645	**-149.69 (-260.56, -38.82)**	**.008**
Age-adjusted	Med	108.07 (-24.20, 240.33)	.109	47.15 (-41.65, 135.96)	.298
	High	212.49 (78.02, 346.96)	.002	86.30 (-5.26, 177.85)	.065
Multivariable-adjusted	Med	83.76 (-41.76, 209.28)	.191	-15.82 (-98.61, 66.97)	.708
	High	181.30 (52.71, 309.89)	.006	18.19 (-67.62, 104.00)	.677
PFOS					
Unadjusted	Med	135.53 (-13.34, 284.39)	.074	-76.68 (-184.96, 21.60)	.165
	High	**-190.78 (-341.75, -39.80)**	**.013**	**-333.91 (-442.31, -225.52)**	**<.001**
Age-adjusted	Med	314.04 (181.67, 446.40)	<.001	13.74 (-75.44, 102.92)	.762
	High	207.85 (65.93, 349.77)	.004	2.96 (-92.73, 98.64)	.952
Multivariable-adjusted	Med	284.00 (158.51, 409.49)	<.001	-30.50 (-113.36, 52.36)	.470
	High	212.04 (76.79, 347.29)	.002	-4.11 (-92.75, 84.53)	.927
PFNA					
Unadjusted	Med	35.12 (-115.83, 186.08)	.648	**-117.68 (-227.24, -8.12)**	**.035**
	High	**-144.09 (-295.20, 7.01)**	**.062**	**-241.86 (-351.54, -132.18)**	**<.001**
Age-adjusted	Med	90.63 (-42.39, 223.65)	.181	-28.41 (-117.18, 60.36)	.530
	High	9.35 (-125.15, 143.85)	.891	-56.03 (-146.41, 34.36)	.224
Multivariable-adjusted	Med	104.73 (-21.35, 230.81)	.103	-22.48 (-104.46, 59.51)	.591
	High	62.12 (-66.04, 190.28)	.342	-32.51 (-116.63, 51.62)	.448
PFHxS					
Unadjusted	Med	75.61 (-75.85, 227.07)	.327	-39.68 (-150.09, 70.72)	.481
	High	52.96 (-98.66, 204.57)	.493	**-186.67 (-296.83, -76.51)**	**.001**
Age-adjusted	Med	159.04 (26.43, 291.65)	.019	34.14 (-54.81, 123.09)	.451
	High	196.41 (62.83, 329.99)	.004	11.18 (-79.45, 101.82)	.809
Multivariable-adjusted	Med	122.44 (-3.91, 248.80)	.058	-8.59 (-91.24, 74.07)	.838
	High	144.57 (15.52, 273.61)	.028	-62.04 (-146.87, 22.80	.152

*In all models, the reference category was the respective low PFAS tertile. Med = Medium
Variables that were adjusted for: age, annual household income and race/ethnicity.
N = 1450

As shown in Table 4, women, when compared with the low tertiles, high exposure in both PFOS and PFNA and medium exposure of PFNA showed a significant decrease in FVC in unadjusted models. In women, PFNA high exposure predicted a decrease in FVC in the age-

adjusted model, showing a trend towards significance (p = 0.104). However, in women, no such association was seen in multivariable adjusted models for any of the four PFASs. In men, only PFNA high exposure showed a significant decrease in FVC in unadjusted models.

Table 4

Association of PFASs Serum Concentration with FVC in NHANES 2011-2012 Participants using Unadjusted and Multivariable Adjusted Linear Regression

		FVC			
		Male		Female	
		B (95% CI)	p-value	B (95% CI)	p-value
PFOA					
Unadjusted	Med	50.63 (-118.96, 220.22)	.558	-14.45 (-142.25, 113.36)	.824
	High	129.61 (-40.49, 299.71)	.135	-95.03 (-222.98, 32.91)	.145
Age-adjusted	Med	79.71 (-81.67, 241.10)	.333	48.28 (-69.05, 165.60)	.419
	High	255.53 (91.46, 419.61)	.002	88.72 (-32.24, 209.68)	.150
Multivariable-adjusted	Med	51.21 (-97.94, 200.36)	.500	-49.55 (-154.49, 55.39)	.354
	High	193.17 (40.37, 345.97)	.013	-10.99 (-119.76, 97.79)	.843
PFOS					
Unadjusted	Med	232.91 (65.64, 400.18)	.006	-53.90 (-179.44, 71.65)	.400
	High	-76.71 (-246.35, 92.93)	.375	**-315.71 (-441.39, -190.03)**	**<.001**
Age-adjusted	Med	359.78 (197.95, 521.61)	<.001	13.01 (-104.55, 130.57)	.828
	High	206.60 (33.09, 380.11)	.020	-66.48 (-192.61, 59.65)	.301
Multivariable-adjusted	Med	307.67 (158.25, 457.09)	<.001	-59.66 (-164.61, 45.29)	.265
	High	180.47 (19.43, 341.51)	.028	-74.78 (-187.05, 37.49)	.191
PFNA					
Unadjusted	Med	-15.14 (-184.43, 154.15)	.861	**-134.43 (-260.81, -8.05)**	**.037**
	High	**-173.39 (-342.86, -3.93)**	**.045**	**-239.92 (-366.44, -113.39)**	**<.001**
Age-adjusted	Med	22.65 (-139.76, 185.07)	.784	-66.60 (-183.65, 50.45)	.264
	High	-65.92 (-233.14, 95.30)	.410	**-98.73 (-217.91, 20.46)**	**.104**
Multivariable-adjusted	Med	39.60 (-110.35, 189.56)	.604	-56.75 (-160.64, 47.13)	.284
	High	8.17 (-144.26, 160.60)	.916	-50.87 (-157.47, 55.73)	.349
PFHxS					
Unadjusted	Med	158.84 (-10.26, 327.94)	.066	30.63 (-96.90, 158.16)	.637
	High	214.11 (44.84, 383,37)	.013	115.80 (-243.05, 11.45)	.074
Age-adjusted	Med	218.58 (57.40, 379.76)	.008	88.06 (-29.20, 205.32)	.141
	High	316.83 (154.47, 479.20)	<.001	38.12 (-81.37, 157.61)	.531
Multivariable-adjusted	Med	146.73 (-3.14, 296.59)	.055	16.40 (-88.31, 121.10)	.759
	High	205.46 (52.41, 358.51)	.009	-79.87 (-187.33, 27.59)	.145

*In all models, the reference category was the respective low PFAS tertile. Med = Medium
Variables that were adjusted for: age, annual household income and race/ethnicity.
N = 1450

When compared with low PFOA, PFOS, and PFHxS tertiles, in men, high exposure showed a decrease in FEV1/FVC in unadjusted models (Table 5) with PFOA trending towards significance (p = .086). For women, all four PFASs, in high exposure tertiles predicted decrease in FEV1/FVC for unadjusted models, as well as medium exposure of PFHxS. Also in women, medium PFHxS exposure showed a decrease in FEV1/FVC in the age-adjusted model, trending towards significance (p = .053). However, in neither men nor women, was any such association seen in multivariable adjusted models. Results did not change in analysis using continuous log transformed PFASs variables.

Table 5

Association of PFASs Serum Concentration with FEV1/FVC in NHANES 2011-2012 Participants using Unadjusted and Multivariable Adjusted Linear Regression

		FEV1/FVC			
		Male		Female	
		B (95% CI)	p-value	B (95% CI)	p-value
PFOA					
Unadjusted	Med	0.62 (-0.93, 2.18)	.431	-0.74 (-2.22, 0.75)	.331
	High	**-1.37 (-2.93, 0.19)**	**.086**	**-2.90 (-4.38, -1.41)**	**<.001**
Age-adjusted	Med	1.05 (-0.29, 2.40)	.125	0.23 (-1.02, 1.49)	.716
	High	0.50 (-0.87, 1.87)	.478	-0.06 (-1.35, 1.24)	.929
Multivariable-adjusted	Med	0.98 (-0.34, 2.30)	.145	0.70 (-0.52, 1.93)	.260
	High	0.87 (-0.48, 2.22)	.207	0.29 (-0.98, 1.56)	.658
PFOS					
Unadjusted	Med	-1.22 (-2.76, 0.31)	.118	-1.08 (-2.57, 0.41)	.154
	High	**-3.05 (-4.61, -1.49)**	**<.001**	**-2.89 (-4.38, -1.40)**	**<.001**
Age-adjusted	Med	0.66 (-0.70, 2.01)	.344	0.10 (-1.16, 1.35)	.877
	High	1.15 (-0.31, 2.60)	.123	1.50 (0.16, 2.85)	.029
Multivariable-adjusted	Med	0.87 (-0.46, 2.20)	.198	0.55 (-0.68, 1.77)	.381
	High	1.71 (0.28, 3.15)	.019	1.49 (0.18, 2.80)	.026
PFNA					
Unadjusted	Med	1.23 (-0.33, 2.78)	.123	-0.56 (-2.05, 0.93)	.463
	High	-0.04 (-1.60, 1.52)	.958	**-1.77 (-3.26, -0.28)**	**.020**
Age-adjusted	Med	1.84 (.50, 3.18)	.007	0.57 (-0.68, 1.82)	.372
	High	1.66 (0.30, 3.02)	.017	0.58 (-0.70, 1.86)	.372
Multivariable-adjusted	Med	1.85 (0.54, 3.17)	.006	0.51 (-0.70, 1.72)	.409
	High	1.50 (0.16, 2.84)	.028	0.10 (-1.14, 1.35)	.871
PFHxS					
Unadjusted	Med	-1.06 (-2.61, 0.50)	.182	**-2.13 (-3.61, -0.65)**	**.005**
	High	**-2.42 (-3.97, -0.86)**	**.002**	**-3.31 (-4.79, -1.83)**	**<.001**
Age-adjusted	Med	-0.19 (-1.54, 1.17)	.788	**-1.24 (-2.49, 0.02)**	**.053**
	High	-0.92 (-2.28, 0.44)	.185	-0.91 (-2.19, 0.37)	.162
Multivariable-adjusted	Med	0.25 (-1.08, 1.58)	.708	-0.77 (-2.00, 0.45)	.216
	High	-1.22 (-1.48, 1.24)	.860	-0.24 (-1.50, 1.02)	.706

*In all models, the reference category was the respective low PFAS tertile. Med = Medium
Variables that were adjusted for: age, annual household income and race/ethnicity.
N = 1450

Discussion

Overall, we observed a consistent statistically significant negative association between lung function and high PFAS exposure in females and some association in males in the unadjusted models. We did not observe an association that was consistently significant in the age-adjusted and multivariable adjusted models.

One of the possible explanations of the above results could be that PFASs are endocrine disruptors (ED) and ED can impact males and females differently. Several published studies report gender dependent differences for PFASs related impacts, for example in a study by Byrne et al. (2018), a positive association between PFNA and PFOS with free T_3 (triiodothyronine) was noted in females, conversely a negative association was seen with male free T_3. In a separate study (Jain & Ducatman, 2019), PFNA and PFOA were positively associated with low-density lipoprotein cholesterol (LDL) and total cholesterol in obese males, however PFNA and PFDA (perfluorodecanoic acid) were positively associated with LDL and total cholesterol in obese females.

The different associations between PFASs and lung function across genders noted in this study could be due to the differences in male and female lung function. The dissimilarities in lung structure and function between males and females start at the lung development prenatal phase (Carey et al., 2007; LoMauro & Aliverti, 2018). Female lungs mature sooner than males in the prenatal phase (Carey et al., 2007; LoMauro & Aliverti, 2018) and at birth, females have smaller lungs with fewer respiratory bronchioles (LoMauro & Aliverti, 2018). Males have bigger lungs than females after puberty meaning that males have a larger total number of alveoli thus they have a larger alveolar surface area (Carey et al., 2007; LoMauro & Aliverti, 2018). Male's lung shapes are pyramidal whereas females have a more prismatic lung shape (LoMauro &

Aliverti, 2018) and recoil pressure of lungs differ due to the size of the lungs and the maximum descending forces.

Other evidence also supports different impact of PFASs on male and female lung function. Qin et al. (2017) reported an association between PFAS exposure and impaired lung function in only male children. Although they believed that their sample size for females was too small, resulting in a significant association only for males (Qin et al., 2017). Sex hormones may impact the gender specific relationship between PFASs and lung function. Zhou et al. (2017) reported that in asthmatic children, PFASs had a negative association with testosterone levels and a positive association with estradiol levels.

Relatively more studies are available on animals that tested the respiratory effects caused by PFASs. In a study by Ye et al. (2012), PFAS exposure was linked with neonatal mortality in mice, which was caused by under-developed lungs. In a separate study of mice pups, exposure to PFAS altered airway function, induced airway inflammation and increased the airway response (Qin et al., 2017).

Our study was internally valid, because we addressed chance, confounding, and bias. Chance is not an explanation of our findings; our results consistently showed negative associations between different PFASs and FEV1, FVC, and FEV1/FVC in unadjusted models of females. For example, the B-value and 95% confidence interval (CI) of PFOA, showed a negative association in the unadjusted models for FEV1, -149.69 (-260.56, -38.82), $p = .008$. This negative association showed up consistently across the female lung function outcomes such as PFOA in unadjusted models with FEV1/FVC, and PFOS with FVC. Besides a valid association between PFASs exposure and lung function, other possible explanations for this finding could include bias and residual confounding. We adjusted for many known confounders,

except smoking. This was due to the complexity of methods utilized to collect smoking data in NHANES 2011 to 2012. However, there could still be unmeasured confounders that bias the observed 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 data from 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. Our study was externally valid and can be applied to the general U.S. population; both genders and different ethnicities, and a wide range of socio-economic strata, were taken into account.

According to the well-defined Hill's epidemiology criteria of causality (Crislip, 2010) exposure should precede outcome could not be met as NHANES is a cross sectional study. This study did have a dose response relationship between the exposure (PFASs: high compared to low) and the lung function. For almost all PFASs, in unadjusted models in females high exposure vs. low exposure was associated with poorer lung function. But among those PFASs that had significantly strong negative association with lung function, even the medium tertile of exposure in unadjusted models showed significant decrement in lung performance. This association was noted for PFNA in with FEV1, PFNA with FVC and PFHxS with FEV1/FVC ratio. Another causality criteria is consistency; we had consistent results for female lung function across all three types of spirometry measures in the unadjusted models; high exposure of PFNA was found to be significant in all three spirometry measures, high exposure in PFHxS was found to be significant in two spirometry measures (FEV1 & FEV1/FVC). Our study also had biological plausibility, as it known that PFASs exposure increases airway inflammation (Qin et al., 2017).

Strengths/Limitations

One of the strengths of this study is that we used nationally representative data from a large, well known cross sectional study (NHANES). Some limitations of the study are not accounting for smoking as a confounder.

Conclusion

PFASs exposure was associated with decreased lung function in females in unadjusted models among a diverse population of participants from the NHANES 2011 to 2012 data. PFASs exposure is a public health concern due to its wide spread use in consumer products and health implications. More research is needed to explore association between PFASs exposure and lung function because the lungs are one of the main tissues where PFAS accumulate (Pérez et al., 2013).

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Appendix A: NHANES Spirometry Exclusion Questions

- SPQ.010 Does SP [the participant] have a painful ear infection?
- SPQ.020 Have you ever had eye surgery? (Do not include cosmetic surgery on the eyelid or skin around the eye.)
- SPQ.030 Was the eye surgery in the last 3 months?
- SPQ.040 Have you ever had open chest or abdominal surgery?
- SPQ.050 Was the open chest or abdominal surgery in the last 3 months?
- SPQ.060 Did you or anyone in your household have tuberculosis in the past year?
- SPQ.070a Has a doctor or other health professional told you that you had an aneurysm?
- SPQ.070b Has a doctor or other health professional told you that you had a collapsed lung?
- SPQ.070c Has a doctor or other health professional told you that you had a detached retina?
- SPQ.070d Has a doctor or other health professional told you that you had a stroke?
- SPQ.070e Has a doctor or other health professional told you that you had a heart attack?
- SPQ.080 Did this stroke happen in the last 3 months?
- SPQ.090 Was your heart attack in the last 3 months?
- SPQ.100 In the past month, have you coughed up blood?

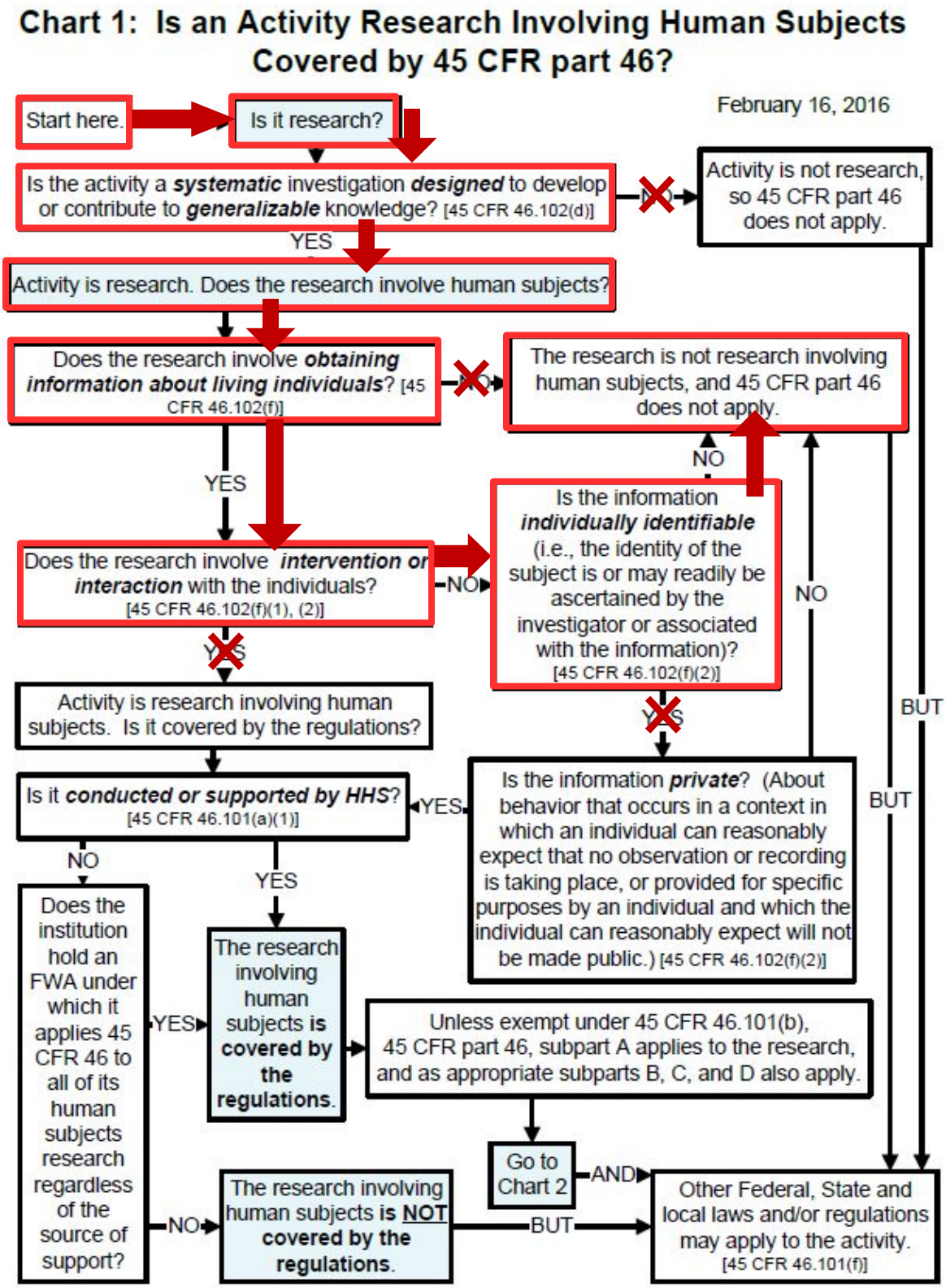
Appendix B: NHANES Variable Names Table

NHANES Variable Name	Variable	Description
LBXPFOA	Serum PFAS Level	Perfluorooctanoic Acid (PFOA)
LBXPFOS	Serum PFAS Level	Perfluorooctane Sulfonic Acid (PFOS)
LBXPFNA	Serum PFAS Level	Perfluorononanoic Acid (PFNA)
LBXPFHS	Serum PFAS Level	Perfluorohexane Sulfonic Acid (PFHxS)
RIAGENDR	Gender	Gender of participant (Female or Male)
RIDAGEYR	Age	Age of participant in years
RIDRETH1	Race/Hispanic Origin	Reported Race/Hispanic Origin of participants
RaceEth3Groups	Race/Hispanic Origin	Recode of RIDRETH1 into three groups of Race/Hispanic origin
INDHHIN2	Income	Annual Household Income
Income3lvl	Income	Recode of INDHHIN2 into three groups of income
SPXNFEV1	FEV1 Test	Baseline FEV 1 (mL)
SPXNFVC	FVC Test	Baseline FVC (mL)
FEV1_FVC	FEV1/FVC	Computed variable taking FEV1 diving that by FVC and multiplying it by 100 for a %

Note: NHANES=National Health and Nutrition Examination Survey, PFAS=Perfluoroalkyl Substance

Source: Centers for Disease Control and Prevention, National Center for Health Statistics (CDC NCHS), 2018.

Appendix C: Human Subjects Regulations Decisions Chart



Appendix D: List of Competencies Met in Integrative Learning Experience

CEPH Foundational Competencies

Evidence-based Approaches to Public Health
2. Select quantitative and qualitative data collection methods appropriate for a given public health context
3. Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate
4. Interpret results of data analysis for public health research, policy or practice
Communication
19. Communicate audience-appropriate public health content, both in writing and through oral presentation

WSU MPH Population Health Concentration Competencies

3. Demonstrate the ability to contextualize and integrate knowledge of specific population health issues.
4. Address diversity when evaluating population health issues related to improving population health, reducing disparities, or increasing equity.