



Perfluoroalkyl substances exposure and hearing impairment in US adults

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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) are widely applied in consumer and industrial products such as nonstick cookware, waterproof clothing, food packaging materials, and fire-fighting foams. These “forever chemicals” are hypothesized to impact neurobehavioral functions. Yet no previous study has explored the role of PFAS on audiometrically determined hearing impairment (HI).

Objectives: To investigate the associations of serum concentrations of perfluoroalkyl substances with low-frequency HI (LFHI) and high-frequency HI (HFHI) in US adults.

Methods: We evaluated the cross-sectional associations in 2371 adults aged 20–69 years who participated in the National Health and Nutrition Examination Survey (NHANES) 2003–2004, 2011–2012 and 2015–2016; and 449 adults aged ≥ 70 years from NHANES 2005–2006 and 2009–2010. Serum concentrations of perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), were measured using solid-phase extraction coupled to High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry. LFHI was defined as a pure-tone average (PTA) of thresholds across 0.5–1.2 kHz > 25 dB; HFHI defined as a PTA across 3–4–6 kHz > 25 dB in the worse ear. Survey-weighted logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) with adjustment for age, age-squared, sex, race/ethnicity, education, poverty-to-income ratio, body mass index, smoking status, exposures to occupational, recreational and firearm noises, and NHANES cycles.

Results: There were no significant associations when perfluoroalkyl variables were fitted as a linear (log-transformed) term. However, statistically significant associations of HFHI with PFNA (OR = 1.70, 95% CI: 1.13–2.56) and PFDA (OR = 1.75, 95% CI: 1.00–3.05) were observed when comparing participants with serum concentrations ≥ 90 th vs. < 90 th percentiles of PFNA (90th percentile = 1.8 ng/mL) and PFDA (90th percentile = 0.5 ng/mL), respectively, in adults aged 20–69 years. No significant associations were observed for other compounds in adults aged 20–69 years and for all compounds in adults ≥ 70 years.

Conclusions: Our study does not provide strong evidence to support the ototoxicity of PFAS exposure. Non-linear threshold dose-response associations between serum concentrations of PFNA and PFDA and HFHI need further investigation.

1. Introduction

Hearing loss is a major health concern affecting over 466 million people worldwide (World Health Organization, 2019). It is an often underestimated chronic condition that negatively impact social, functional, and psychological well-being of a person, and general quality of life (Arlinger, 2003). The disease also places a significant financial burden on society, as it is expected that moderate to severe hearing loss would cost the health-care sector \$67–110 billion globally (World Health Organization, 2017). The potential ototoxic effects of chemicals have been reported among workers (Morata, 2007; Sliwińska-Kowalska

et al., 2003) and general populations (Choi et al., 2012; Choi and Park, 2017; Park et al., 2010; Shiue, 2015).

Per- and polyfluoroalkyl substances (PFAS) are a group of persistent anthropogenic chemicals, which are widely applied in fire-fighting foams; nonstick cookware, weatherproof clothing, surface protectants, food packaging, and other consumer products. Widespread use and extreme resistance to degradation have resulted in the ubiquitous presence of those chemicals in the general environment. These compounds were detected in 194 of 4864 water supplies, affecting up to 110 million residents in the United States (US) (Environmental Working Group, 2018). PFAS are ubiquitous environmental toxicants to which humans

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are exposed on a daily basis (Trudel et al., 2008).

As a group of polyhalogenated compounds, PFAS is associated with metabolic disorders (Jiang et al., 2015), endocrine disruption (Jensen and Leffers, 2008), and developmental and neurobehavioral toxicity (Mariussen, 2012). Thyroid systems appears to be particularly vulnerable to disruption by PFAS with a reduction in total thyroxine (T4) concentrations following exposure in humans (Ballesteros et al., 2017; Kim et al., 2018). Animal data suggest that halogenated hydrocarbon-induced hearing loss is the sequelae of thyroid gland dysfunctions caused by these substances (Crofton and Zoeller, 2005; Goldey et al., 1995; Zoeller, 2005). In addition, a recent mouse model detected the existence of peroxisome proliferator-activated receptors (PPARs), ligand-activated transcription factors that regulate gene expression, in diverse structures of the cochlea including both outer hair cells (OHCs) and inner hair cells (IHCs), similar to levels in brain and liver (Sekulic-Jablanovic et al., 2017). Activation of PPARs by PFAS exposure modulate cell proliferation and differentiation, as well as lipid and glucose homeostasis (Intrasuksri et al., 1998; Kennedy et al., 2004; Rosen et al., 2017; Shipley et al., 2004).

While studies have suggested possible associations between perfluoroalkyls and self-reported hearing impairment (HI) (Shiue, 2015), no study has explored the effects of perfluoroalkyls on audiometrically measured HI. This cross-sectional study aimed to examine the associations between perfluoroalkyl exposures and HI in US adults who participated in the National Health and Nutrition Examination Survey (NHANES).

2. Methods

2.1. Study participants

The NHANES is an ongoing survey, conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), to measure the health and nutrition status of the civilian noninstitutionalized U.S. population ≥ 2 months of age. The NHANES study protocol is described in detail on the NCHS website <https://www.cdc.gov/nchs/nhanes/index.htm>. Informed consent forms are obtained from all NHANES participants.

Our study used five cycles of NHANES data for the survey periods of 2003–2004, 2005–2006, 2009–2010, 2011–2012, and 2015–2016. Different age groups were measured in different subsamples of survey cycles (see details in Supplemental Material Table S1). Therefore, our study included a total of 3184 adults with complete perfluoroalkyl measurements and audiometry: 2669 adults aged 20–69 years from NHANES 2003–2004, 2011–2012, and 2015–2016; 515 adults aged ≥ 70 years from NHANES 2005–2006 and 2009–2010. In NHANES 2007–2008 and 2013–2014, audiometry tests were not included. Details of our study design are shown in Supplemental Material Fig. S1. We excluded a total of 364 participants (11.4%) because of missing data in core covariates. Therefore, our final analytic sample included 2820 participants, including 2371 adults aged 20–69 years and 449 adults ≥ 70 years.

2.2. Chemical measurements

Serum perfluoroalkyl concentrations were measured using solid phase extraction coupled to High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry (online SPE-HPLC-TIS-MS/MS). Detailed description of the laboratory method is publicly available elsewhere (Calafat and Pirkle, 2013). Analytes for the laboratory tests included perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorodecanoic acid (PFDA), perfluorobutane sulfonic acid (PFBS), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoA). Five perfluoroalkyls with detection rates $> 70\%$ (PFHxS,

PFOS, PFOA, PFNA, and PFDA) were considered in the final analyses. The values below the limit of detection (LOD) were replaced by LOD divided by square root of 2 (Centers for Disease Control and Prevention, 2014).

2.3. Hearing impairment

All audiometric testing sections were performed by a trained technician in sound-isolating booths at a mobile examination center (MEC). Participants using hearing aids who were not able to remove them for testing and those who had intolerable ear pain at the time of the exam were excluded from the audiological exam. Thresholds were obtained using a pulsed-tone stimulus as per Modified Hughson-Westlake Procedure (Carhart and Jerger, 1959). Pure-tone air conduction hearing thresholds were obtained for both ears at seven inter-octave frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) over an intensity range of -10 to 110 dB (dB). Higher frequencies were perceived as higher pitches. Retest thresholds were obtained at 1 kHz for each ear to confirm consistency; the second 1 kHz threshold was used in this analysis if there was no more than a 10 dB difference between them. The audiometric testing protocols are available elsewhere (Centers for Disease Control and Prevention, 2003).

We defined two types of HI, i.e. low-frequency hearing impairment (LFHI) and high-frequency hearing impairment (HFHI) as per World Health Organization guidelines (World Health Organization, 1991). LFHI was defined as a pure tone average (PTA) of thresholds across 0.5, 1, and 2 kHz > 25 dB; and HFHI was defined as a PTA of thresholds across 3, 4, and 6 kHz > 25 dB in the worse ear (World Health Organization, 1991).

2.4. Covariates

Potential confounders considered in the analyses included age, sex, race/ethnicity, education, a ratio of household income to poverty-income ratio (PIR), body mass index (BMI), smoking status, noise exposures (i.e. occupational, firearm, and recreational noise), and NHANES cycles. A squared term of age was used to capture a non-linear relationship between age and the outcomes. Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, and other racial/ethnic groups. Mexican American, other Hispanics and others were combined due to small sample sizes of these subgroups. Covariates were selected based on previous studies (Choi et al., 2012; Y.-H. Choi and Park, 2017; Ding et al., 2020; Park et al., 2019, 2010).

Information on demographic variables, socioeconomic status, smoking, and noise exposures were obtained during in-home interviews. Data on BMI were collected at a MEC by trained health technicians, as a measure dividing weight in kilogram by the square of height in meter (continuous, kg/m^2). Education was categorized as less than high school, high school graduate or equivalent, some college or associate degree, and college graduate or above. PIR was defined as the ratio of family income divided by the poverty threshold adjusted for family size and annual inflation. A PIR below 1 indicates that the family is living below the poverty threshold. Smoking status was categorized as self-reported current smoker, former smoker, or nonsmoker.

Noise exposures were also based on self-report. Relevant questionnaire differences during NHANES 2003–2012 were: 1) work-related noise exposure in the 2003–2004 NHANES was defined as “loud job noise ever exposed for at least three months”, in the 2005–2010 NHANES as “ever had a job exposure to loud noise for 5 or more hours a week”, and in the 2011–2012 and 2015–2016 NHANES as “ever had a job exposure to loud noise for 4 or more hours a day, several days a week”. 2) Firearm exposure in the 2003–2004 NHANES was defined as “firearm noise exposure outside work for an average of at least once a month for a year”, and in the 2005–2012 and 2015–2016 NHANES as “ever used firearm for any reason”. Recreational noise exposure was defined as “exposed to loud noise or listened to music with headphones

in the past 24 h” in the 2003–2012 NHANES cycles, and in the 2015–2016 NHANES as “Outside of a job, ever been exposed to very loud noise or music for 10 or more hours a week”.

2.5. Statistical analyses

Complex survey design was considered using the appropriate sub-sample weights, strata and primary sampling units per NHANES recommendation (Center for Health Statistics, 2011). Survey-weighted univariate statistics were computed and differences in the distributions of demographics, socioeconomic status, noise exposures, smoking history, and diabetes and hypertension status were tested with the *t*-test for continuous characteristics or chi-square test for categorical characteristics by HI status. We also computed survey-weighted least square geometric means and 95% confidence intervals (95% CIs) for serum PFHxS, PFOS, PFOA, PFNA and PFDA concentrations across various sub-populations, after adjusting for age, sex, race/ethnicity, education, poverty-income ratio, smoking status, BMI, noise exposures and NHANES cycles.

We examined the association of serum concentrations of perfluoroalkyl with LFHI and HFHI using survey-weighted logistic regression models, among adults aged 20–69 years (NHANES, 2003–2004, 2011–2012, and 2015–2016) and those ≥ 70 years (NHANES, 2005–2006 and NHANES, 2009–2010), separately. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated with adjustment for age, age squared, sex, race/ethnicity, education, PIR, smoking status, BMI, noise exposure at work, recreational noise exposure, noise exposure through firearm, and NHANES cycles.

Generalized additive models (GAMs) with penalized splines were applied to check whether the associations are linear or nonlinear. Fig. 1 clearly shows the non-linear dose-response relationships with thresholds between serum concentrations of PFNA and PFDA and adjusted ORs of HFHI. Concentrations of PFNA and PFDA above certain levels were positively associated with increased risks of HFHI. We evaluated various knot locations at different deciles based on the visual inspection and chose the best knot location with the lowest Akaike Information Criterion (AIC) values, which suggested the 90th percentile as the cutoff point for PFNA and PFDA.

We, therefore, used two approaches to fitting perfluoroalkyl variables.

- 1) Perfluoroalkyl variables were log-transformed with base 2 and ORs of HI associated with per doubling increase in each perfluoroalkyl variable were reported.
- 2) Perfluoroalkyl variables were dichotomized at the 90th percentile and ORs of HI comparing participants with serum concentrations ≥ 90 th vs. < 90 th percentiles were reported.

We also explored the associations between perfluoroalkyls and hearing thresholds at each test frequency and calculated adjusted least square means of hearing thresholds comparing perfluoroalkyl concentrations ≥ 90 th vs. < 90 th percentiles. All statistical analyses were performed using SAS survey procedures (version 9.4. SAS Institute Inc.). Sampling weight-applied smoothing plots were created using the GAM function with penalized spline in the ‘MGCV’ package in R (version 3.6.0. R Foundation for Statistical Computing).

2.6. Sensitivity analyses

Several sensitivity analyses for different multivariate models and outcomes were conducted to test whether our results were robust to various alternative modeling. First, for the associations in adults aged 20–69 years, we used data from the most recent NHANES cycles 2011–2012 and 2015–2016 and dropped NHANES 2003–2004 to exclude the possibility of the observed relationships explained by declines in HI prevalence and serum perfluoroalkyl concentrations. Second, we

additionally adjusted for blood lead and blood cadmium in the analyses because previous studies have found cadmium and lead as potential risk factors for hearing impairment (Choi et al., 2012; Choi and Park, 2017; Park et al., 2010). In addition, we did not consider diabetes and hypertension as confounders in the primary analyses in case of over-adjustment bias because perfluoroalkyl might contribute to the development of diabetes (Cardenas et al., 2017; He et al., 2018; Sun et al., 2018), and abnormal blood pressure (Bao et al., 2017; Min et al., 2012; Steenland et al., 2010). Therefore, as a sensitivity analysis, we additionally adjusted for diabetes and hypertension status.

3. Results

Table 1 shows survey-weighted participant characteristics of the U.S. adults 20–69 years of age stratified by HI status. Of 2371 adults, 721 had any form of HI (sample-weighted prevalence = 30.5%). Participants with HFHI were 14.8 years older on average ($P < .0001$), more likely to be male ($P < .0001$), non-Hispanic white ($P < .0001$), had attained high school or lower level of education ($P = 0.01$), and had higher BMI ($P = 0.003$). People with HFHI were also more likely to be former or current smokers ($P < .0001$). Participants with any HFHI and HFHI were more likely to experience firearm noise ($P < .0001$) and occupational noise ($P = 0.002$). Participants with HFHI also tended to have higher prevalence of type-2 diabetes ($P < .0001$) or hypertension ($P < .0001$) conditions. Similar differences were also observed for LFHI. In addition, compared to those without HI, participants with HI had higher median concentrations of PFHxS, PFOS, PFOA and PFNA. Participant characteristics of adults ≥ 70 years are shown in Supplemental Materials Table S2. We did not observe significant differences by HI status, possibly due to the small sample size of participants without HI ($N = 26$).

Survey-weighted least square geometric means and ratio differences in PFAS concentrations by participant characteristics are shown in Table 2, after controlling for age, sex, race/ethnicity, education level, poverty-income ratio, smoking status, body mass index, noise exposures (occupational, recreational, and firearm noise) and NHANES cycles. Serum concentrations of PFHxS, PFOS, PFOA, PFNA and PFDA were significantly higher among adults 60–69 years vs. those 20–39 years of age, males vs. females, and ever vs. never smoker, after adjusting for covariates. Serum perfluoroalkyl concentrations also differed significantly by racial/ethnic groups. Non-Hispanic white had significantly higher serum concentrations of PFOA while lower concentrations of PFNA and PFDA, compared to other racial/ethnic groups. Non-Hispanic black had significantly higher serum concentrations of PFOS. Interestingly, persons who received college education and higher had significantly higher concentrations of PFHxS. Former and current smokers had significantly higher concentrations of PFOA and PFOS compared to never smokers. Occupational, firearm and recreational noises were not associated with perfluoroalkyl concentrations.

The associations between perfluoroalkyls and HI in adults aged 20–69 years are presented in Table 3. There were no significant associations when perfluoroalkyl variables were fitted as a linear (log-transformed) term. However, statistically significant associations of HFHI with PFNA (OR = 1.70, 95% CI: 1.13–2.56) and PFDA (OR = 1.75, 95% CI: 1.00–3.05) were observed when comparing participants with serum concentrations ≥ 90 th vs. < 90 th percentiles of PFNA (90th percentile = 1.8 ng/mL) and PFDA (90th percentile = 0.5 ng/mL). No significant associations were observed for other compounds. Fig. 2 presents the associations between hearing thresholds at each frequency and levels of perfluoroalkyl exposures (≥ 90 th vs. < 90 th percentile) in the covariate-adjusted models. No significant differences were detected for PFAS compounds, although participants with higher concentrations of PFNA and PFDA tended to have elevations in their hearing thresholds at 3, 4, 6 and 8 kHz test frequencies. No significant associations were observed in adults aged ≥ 70 years (Supplemental Material Table S3).

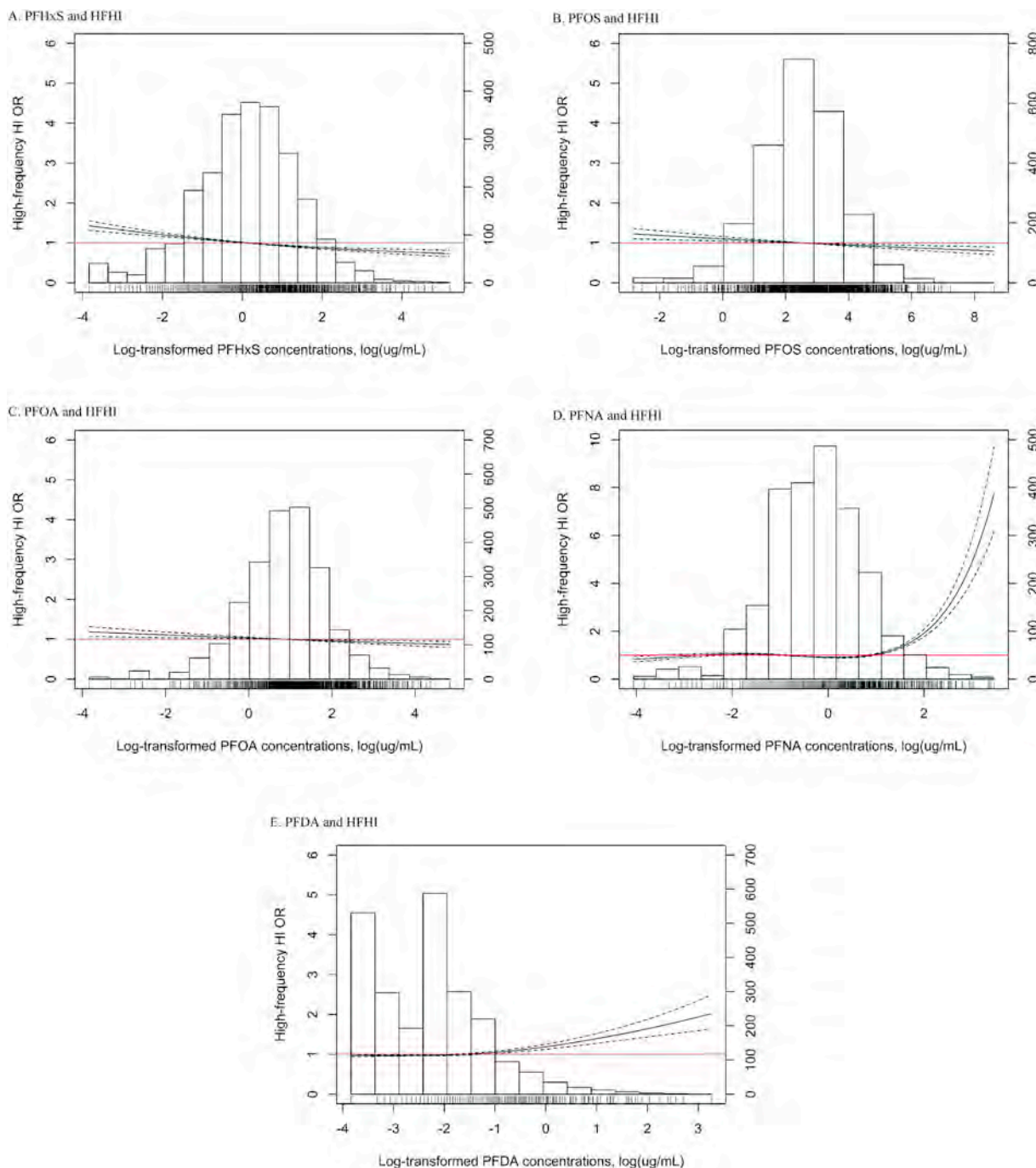


Fig. 1. Smoothing curves of the relationships between serum concentrations of PFAS and adjusted odds ratios (95% confidence intervals) of high-frequency hearing impairment (HI) using generalized additive models with penalized splines. A. PFHxS and HFHI; B. PFOS and HFHI; C. PFOA and HFHI; D. PFNA and HFHI; E. PFDA and HFHI. The models were adjusted for age, age square, sex, race/ethnicity, education level, poverty-income ratio, smoking status, body mass index, noise exposures (occupational, recreational, and firearm noise), and NHANES cycles. Survey weights were considered in the analyses.

The results remained similar with the recent NHANES cycles 2011–2012 and 2015–2016 (Supplemental Material Table S4). The adjusted OR of having HFHI conditions was 1.70 (95% CI: 1.12–2.57) for PFNA and 1.78 (95% CI: 1.03–3.09) for PFDA, comparing serum concentrations ≥ 90 th vs. < 90 th percentile, with an additional adjustment for diabetes status and hypertension (Supplemental Materials Table S5). Similar findings were observed after additionally controlling for blood lead and blood cadmium (Supplemental Materials Table S6).

4. Discussion

Our study examined the associations between perfluoroalkyl serum concentrations and audiometrically assessed HI in the U.S. adults using nationally representative data. We observed non-linear threshold dose-response relationships of HFHI with PFNA and PFDA in adults aged 20–69 years after adjusting for covariates and these relationships were robust in several sensitivity analyses. We did not detect significant log-linear relationships (i.e., a log-transformed variable fitted as a linear term). No significant associations were observed in adults ≥ 70 years

Table 1
Survey-weighted characteristics of the U.S. population age 20–69 years overall and by status of hearing impairment (HI).^{a,b}

Characteristic	Total (N = 2371)	No HI (N = 1650)	Any HI	
			HFHI (n = 709)	LFHI (n = 204)
Age (years), mean (SE)	43.5 (0.5)	39.0 (0.6)	53.8 (0.7)	56.2 (0.9)
BMI (kg/m ²), mean (SE)	29.0 (0.2)	28.6 (0.3)	30.0 (0.3)	32.0 (0.7)
Sex, % (SE)				
Male	48.7 (1.2)	42.7 (1.4)	63.1 (2.0)	52.3 (4.8)
Female	51.3 (1.2)	57.3 (1.4)	36.9 (2.0)	47.7 (4.8)
Race/ethnicity, % (SE)				
Non-Hispanic White	66.5 (2.5)	63.2 (2.7)	73.9 (2.8)	74.6 (3.7)
Non-Hispanic Black	10.9 (1.4)	12.5 (1.6)	6.9 (1.3)	7.9 (1.7)
Other Race/ethnicity	22.6 (1.9)	24.3 (2.0)	19.2 (2.2)	17.5 (3.1)
Education, % (SE)				
< High School	11.3 (1.1)	9.6 (1.1)	15.4 (1.7)	13.6 (2.9)
High School or Equivalent	20.4 (1.4)	19.4 (1.5)	22.7 (2.5)	22.2 (4.4)
Some College	34.6 (1.8)	36.3 (2.2)	30.1 (2.8)	38.5 (5.3)
College Graduate or Above	33.7 (2.8)	34.7 (2.9)	31.8 (3.9)	25.7 (5.1)
Poverty-to-income ratio, % (SE)				
< 1.0	13.7 (1.2)	12.6 (2.0)	13.9 (1.5)	13.7 (1.5)
≥ 1.0	86.3 (1.2)	87.4 (2.0)	86.1 (1.5)	86.3 (1.5)
Cigarette Smoking, % (SE)				
Never Smoker	20.5 (0.8)	20.2 (1.2)	20.9 (2.4)	14.0 (3.3)
Former Smoker	22.1 (1.1)	18.6 (1.1)	30.7 (2.6)	29.0 (5.9)
Current Smoker	57.4 (1.2)	61.2 (1.5)	48.4 (2.2)	57.0 (6.1)
Occupational noise exposure, % (SE)				
Yes	34.6 (1.6)	31.3 (2.0)	42.2 (2.6)	40.9 (4.2)
No	65.4 (1.6)	68.7 (2.0)	57.8 (2.6)	59.1 (4.2)
Firearm noise exposure, % (SE)				
Yes	45.8 (2.2)	42.0 (2.1)	55.3 (3.3)	53.1 (5.1)
No	54.2 (2.2)	58.0 (2.1)	44.7 (3.3)	46.9 (5.1)
Recreational noise exposure, % (SE)				
Yes	15.1 (1.0)	15.4 (1.3)	14.5 (1.6)	15.3 (4.0)
No	84.9 (1.0)	84.6 (1.3)	85.5 (1.6)	84.7 (4.0)
Type-2 diabetes, % (SE)				
Yes	10.7 (0.9)	6.9 (0.9)	19.7 (1.9)	24.1 (4.4)
No	89.3 (0.9)	93.1 (0.9)	80.3 (1.9)	75.9 (4.4)
Hypertension, % (SE)				
Yes	28.4 (1.4)	22.5 (1.3)	41.7 (2.7)	40.7 (5.2)
No	71.6 (1.4)	77.5 (1.3)	58.3 (2.7)	59.3 (5.2)
NHANES cycles, % (SE)				
2003–2004	8.3 (1.1)	8.9 (1.1)	6.8 (1.5)	6.6 (2.6)
2011–2012	42.0 (2.2)	42.4 (2.5)	40.9 (3.2)	39.3 (5.3)
2015–2016	49.7 (2.3)	48.7 (2.5)	52.3 (3.4)	54.0 (5.2)
PFAS concentrations (ng/mL), Median (IQR) ^c				
PFHxS	1.3 (0.7–2.1)	1.2 (0.7–2.0)	1.4 (0.8–2.3)	1.3 (0.7–2.6)
PFOS	6.2 (3.5–10.5)	5.6 (3.3–9.9)	7.3 (4.4–12.5)	7.6 (4.2–11.0)
PFOA	2.0 (1.3–2.9)	1.9 (1.2–2.9)	2.1 (1.4–3.1)	2.2 (1.4–2.9)
PFNA	0.7 (0.5–1.1)	0.7 (0.5–1.0)	0.8 (0.5–1.3)	0.8 (0.5–1.3)
PFDA	0.2 (< LOD-0.3)	0.2 (< LOD-0.3)	0.2 (< LOD-0.3)	0.2 (< LOD-0.3)

Abbreviations: BMI, body mass index; GM, geometric mean; GSE, geometric standard error; IQR, interquartile range; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SE, standard error.

^a Data from the National Health and Nutrition Examination Survey, 2003–2004, 2011–2012 and 2015–2016.

^b Complex survey design were considered in the analyses.

^c Geometric mean and SE were calculated due to skewed distributions of serum PFAS concentrations.

possibly due to the small sample size of older population. To our knowledge, this is the first report to link serum perfluoroalkyls and audiometric measures among adults, highlighting the importance of exploring the role of perfluoroalkyls on neurobehavioral functions in animals and humans.

The evidence of underlying biological mechanisms linking environmentally relevant PFAS exposure concentrations to the development of HI are limited. PFAS exposures play an important role in PPAR signaling. PPARs, a family of ligand-regulated nuclear hormone receptors, have been identified as a key player in the mode of action for PFAS toxicity. The chemical structure of PFAS are analogous to fatty acids and both can activate PPARs and further induce endocrine disruption (Kraugerud et al., 2011; Pedersen et al., 2016), as well as disturbance of lipid and glucose metabolism, inflammation and adipocyte differentiation (Berger et al., 2005; Staels and Fruchart, 2005). Two of the PPAR family members, PPAR α and PPAR γ , were detected in the inner ears of neonatal and adult mice, and alterations in PPARs could impact inner and outer HC apoptosis (Sekulic-Jablanovic et al., 2017). Although human PPAR α appears to be less responsive to PFAS exposure than mouse PPAR α , most perfluoroalkyl carboxylates and sulfonates activate PPAR α , and to a lesser extent PPAR γ in mouse and human models (Wolf et al., 2008). The ability to stimulate PPAR α and PPAR γ of the cochlea with PFAS exposures appears to offer an alternative explanation for the observed associations.

Exposures to PFNA and PFDA were associated with higher odds of HFHI in adults aged 20–69 years, while no significant associations were observed for other PFAS compounds. Studies have shown that the differential results may be related to differential transactivity with PPAR signaling pathways. Perfluoroalkyl carboxylates (e.g. PFOA) is more capable than the corresponding sulfonates (e.g. PFOS) in activating PPAR α in mouse and human models (Takacs and Abbott, 2007; Vanden Heuvel et al., 2006; Wolf et al., 2008). In addition, longer-chain carboxylates such as PFDA and PFNA induced higher activation of PPAR α than PFOA (Wolf et al., 2010, 2008). However, due to the limited evidence of toxicity of various PFAS compounds and especially longer-chain compounds, future studies are needed to explore the differential mechanisms.

Unlike the study by Shiue (2015) in which an increased OR of self-reported hearing disturbances was observed for participants with higher PFOA serum concentrations in NHANES 2011–2012, we did not detect any associations of PFOA with audiometrically assessed hearing loss. Audiometry instead of self-reported information might account for the discrepancies. In addition, we explored the non-linear relationships of HFHI with PFNA and PFDA. Our dose-response relationship is consistent with a threshold effect, suggesting that, if these findings are causal, ototoxicity of these longer-chain perfluoroalkyl carboxylic acids may be activated at certain concentrations and above. These results highlight the need to consider the shape of nonlinear dose-response relationships when studying environmental ototoxic chemicals.

A major strength of this study was the population examined. The NHANES is a complex stratified survey. With sampling weights, strata and units considered in the analyses, our study samples are representative of the general U.S. adults. However, it is difficult to make an inference about the temporal causation of exposures and hearing loss in a cross-sectional study. Given the nationally representative nature of data, however, our results are important and support the need for future research to evaluate perfluoroalkyl exposure as a potential risk factor for hearing impairment. Moreover, we cannot rule out residual confounding by noise environments that cannot be captured by dichotomous indicators for occupational, recreational and firearm exposures. This limitation may be more of a factor for high-frequency notches because this outcome incorporates pure tone thresholds observed across 3–6 kHz, at which excessive noise stimulus affects most (Gates et al., 2000). Other persistent organic pollutants, such as polychlorinated biphenyls (PCBs), have been associated with hearing impairment in U.S. adults (Min et al., 2014). PCBs and PFAS belong to the family of

Table 2 Survey-weighted adjusted least square geometric means (95% confidence intervals, CIs) of perfluoroalkyl substance serum concentrations by participant characteristics and HI status in U.S. Adults 20–69 Years of age.^a

	N (%)	PFOS			PFOA			PFNA			PFDA		
		Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)		
Sociodemographic characteristics													
<i>Age, years</i>													
20–39	1007 (42.5)	Reference	6.78 (6.10–7.53)	Reference	1.98 (1.79–2.20)	Reference	0.70 (0.62–0.78)	Reference	0.18 (0.16–0.20)	Reference	0.18 (0.16–0.20)	Reference	
40–59	932 (39.3)	1.00 (0.88–1.12)	8.90 (7.95–9.97)	1.31 (1.18–1.47)	2.27 (2.06–2.51)	1.15 (1.04–1.27)	0.83 (0.74–0.93)	1.19 (1.06–1.33)	0.21 (0.18–0.23)	1.13 (1.04–1.24)	0.21 (0.18–0.23)	1.13 (1.04–1.24)	
60–69	432 (18.2)	1.37 (1.17–1.59)	12.02 (10.37–13.93)	1.77 (1.52–2.07)	2.71 (2.42–3.04)	1.37 (1.19–1.58)	1.09 (0.94–1.27)	1.57 (1.33–1.85)	0.26 (0.22–0.31)	1.45 (1.23–1.72)	0.26 (0.22–0.31)	1.45 (1.23–1.72)	
<i>Sex</i>													
Male	1169 (49.3)	Reference	11.69 (10.58–12.92)	Reference	2.72 (2.52–2.93)	Reference	0.94 (0.85–1.05)	Reference	0.22 (0.20–0.25)	Reference	0.22 (0.20–0.25)	Reference	
Female	1202 (50.7)	0.53 (0.49–0.58)	6.91 (6.22–7.67)	0.59 (0.55–0.64)	1.95 (1.80–2.12)	0.72 (0.67–0.77)	0.78 (0.71–0.86)	0.83 (0.77–0.89)	0.21 (0.19–0.23)	0.93 (0.87–0.99)	0.21 (0.19–0.23)	0.93 (0.87–0.99)	
<i>Race/ethnicity</i>													
Non-Hispanic White	817 (34.5)	Reference	8.89 (8.11–9.73)	Reference	2.49 (2.30–2.68)	Reference	0.79 (0.72–0.87)	Reference	0.19 (0.17–0.21)	Reference	0.19 (0.17–0.21)	Reference	
Non-Hispanic Black	587 (24.7)	0.90 (0.79–1.03)	10.09 (8.97–11.36)	1.14 (1.04–1.24)	2.24 (2.04–2.46)	0.90 (0.84–0.97)	0.92 (0.82–1.03)	1.17 (1.07–1.27)	0.23 (0.21–0.26)	1.22 (1.11–1.34)	0.23 (0.21–0.26)	1.22 (1.11–1.34)	
Other Race/Ethnicity	967 (40.8)	0.80 (0.70–0.90)	8.09 (7.18–9.12)	0.91 (0.83–1.00)	2.20 (2.02–2.39)	0.89 (0.81–0.97)	0.87 (0.78–0.98)	1.11 (1.01–1.22)	0.22 (0.20–0.25)	1.16 (1.03–1.31)	0.22 (0.20–0.25)	1.16 (1.03–1.31)	
<i>Education</i>													
< HS	433 (18.3)	Reference	9.14 (8.04–10.39)	Reference	2.17 (1.96–2.41)	Reference	0.87 (0.77–0.98)	Reference	0.22 (0.19–0.25)	Reference	0.22 (0.19–0.25)	Reference	
HS or Equivalent	513 (21.6)	0.99 (0.87–1.13)	8.69 (7.65–9.88)	0.95 (0.85–1.06)	2.22 (2.00–2.47)	1.02 (0.93–1.13)	0.83 (0.74–0.94)	0.96 (0.86–1.07)	0.21 (0.19–0.24)	0.98 (0.90–1.08)	0.21 (0.19–0.24)	0.98 (0.90–1.08)	
Some College	777 (32.8)	1.08 (0.95–1.22)	9.16 (8.17–10.27)	1.00 (0.89–1.13)	2.42 (2.22–2.64)	1.11 (1.01–1.23)	0.85 (0.76–0.95)	0.97 (0.87–1.09)	0.20 (0.18–0.22)	0.93 (0.84–1.02)	0.20 (0.18–0.22)	0.93 (0.84–1.02)	
≥College Graduate	648 (27.3)	1.16 (1.02–1.33)	8.96 (8.08–9.93)	0.98 (0.85–1.12)	2.41 (2.21–2.63)	1.11 (0.99–1.24)	0.89 (0.79–1.00)	1.02 (0.91–1.14)	0.23 (0.20–0.26)	1.04 (0.89–1.21)	0.23 (0.20–0.26)	1.04 (0.89–1.21)	
<i>Poverty-to-income ratio</i>													
≥1.0	1854 (78.2)	Reference	9.38 (8.64–10.19)	Reference	2.43 (2.26–2.62)	Reference	0.90 (0.82–0.98)	Reference	0.22 (0.21–0.24)	Reference	0.22 (0.21–0.24)	Reference	
< 1.0	517 (21.8)	0.94 (0.80–1.10)	8.60 (7.48–9.90)	0.92 (0.81–1.04)	2.18 (1.99–2.39)	0.90 (0.82–0.98)	0.82 (0.73–0.93)	0.92 (0.83–1.02)	0.21 (0.18–0.24)	0.92 (0.82–1.02)	0.21 (0.18–0.24)	0.92 (0.82–1.02)	
Lifestyle factors													
<i>Cigarette Smoking</i>													
Never Smoker	494 (20.8)	Reference	7.90 (7.22–8.65)	Reference	2.15 (2.01–2.31)	Reference	0.82 (0.74–0.91)	Reference	0.19 (0.17–0.21)	Reference	0.19 (0.17–0.21)	Reference	
Former Smoker	464 (19.6)	1.12 (0.97–1.29)	9.38 (8.28–10.62)	1.19 (1.08–1.30)	2.41 (2.17–2.69)	1.12 (1.03–1.22)	0.86 (0.76–0.98)	1.05 (0.93–1.18)	0.22 (0.19–0.26)	1.17 (1.02–1.35)	0.22 (0.19–0.26)	1.17 (1.02–1.35)	
Current Smoker	1413 (59.6)	1.03 (0.92–1.15)	9.79 (8.82–10.87)	1.24 (1.15–1.33)	2.35 (2.17–2.55)	1.09 (1.01–1.18)	0.89 (0.80–0.99)	1.08 (0.99–1.18)	0.23 (0.21–0.26)	1.21 (1.12–1.31)	0.23 (0.21–0.26)	1.21 (1.12–1.31)	
Body measures													
<i>BMI, kg/m²</i>													
≤25	710 (29.9)	Reference	9.75 (8.63–11.01)	Reference	2.42 (2.22–2.63)	Reference	0.91 (0.80–1.03)	Reference	0.24 (0.21–0.28)	Reference	0.24 (0.21–0.28)	Reference	
> 25	1661 (70.1)	0.94 (0.87–1.03)	8.71 (7.89–9.61)	0.89 (0.81–0.98)	2.26 (2.09–2.45)	0.93 (0.86–1.01)	0.84 (0.76–0.93)	0.92 (0.83–1.03)	0.20 (0.19–0.23)	0.85 (0.77–0.95)	0.20 (0.19–0.23)	0.85 (0.77–0.95)	
Noise exposures													
<i>Occupational noise exposure</i>													

(continued on next page)

Table 2 (continued)

	N (%)	PFHxS	PFOS	PFOA	PFNA	PFDA	
		ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)	ng/mL (95% CI)	Ratio difference (95% CI)
Yes	815 (34.4)	1.43 (1.25–1.64)	Reference	2.29 (2.11–2.49)	Reference	0.21 (0.19–0.24)	Reference
No	1556 (65.6)	1.35 (1.20–1.52)	0.94 (0.86–1.03)	2.31 (2.13–2.50)	1.01 (0.94–1.09)	0.21 (0.19–0.24)	1.00 (0.90–1.13)
Firearm noise exposure							
Yes	835 (35.2)	1.42 (1.23–1.62)	Reference	2.28 (2.06–2.53)	Reference	0.21 (0.19–0.24)	Reference
No	1536 (64.8)	1.37 (1.21–1.55)	0.97 (0.86–1.08)	2.31 (2.16–2.48)	1.01 (0.92–1.11)	0.21 (0.19–0.24)	1.00 (0.91–1.08)
Recreational noise exposure							
Yes	331 (14.0)	1.42 (1.21–1.67)	Reference	2.37 (2.13–2.64)	Reference	0.20 (0.18–0.23)	Reference
No	2040 (86.0)	1.37 (1.22–1.53)	0.96 (0.84–1.11)	2.23 (2.08–2.40)	0.94 (0.84–1.05)	0.22 (0.20–0.24)	1.08 (0.98–1.20)

Abbreviations: BMI, body mass index; HS, high school; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluoronanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid.

^a Geometric mean and 95% CI were calculated due to skewed distributions of serum PFAS concentrations. Ratio difference and 95% CI were used to calculate the relative difference by participant characteristics compared to the reference group. The analyses were adjusted for age, sex, race/ethnicity, education level, poverty-income ratio, smoking status, body mass index, noise exposures (occupational, recreational, and firearm noise), and NHANES cycles.

Table 3

Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) Comparing Hearing Impairment (low frequency hearing impairment (LFHI) or high frequency hearing impairment (HFHI)) in the Worse Ear with No Hearing Impairment (N = 1650) by PFAS Serum Concentrations in Adults 20–69 years from NHANES 2003–2004, NHANES 2011–2012 and 2015–2016 (N = 2371).^a

Variable	LFHI (N = 204)	HFHI (N = 709)
	OR (95% CI)	OR (95% CI)
PFOS		
Per doubling	0.87 (0.73–1.03)	0.96 (0.85–1.10)
≥ 90th vs. < 90th percentile (19.0 ng/mL)	0.72 (0.29–1.75)	1.31 (0.75–2.27)
PFOA		
Per doubling	0.98 (0.73–1.32)	0.97 (0.82–1.14)
≥ 90th vs. < 90th percentile (4.2 ng/mL)	1.40 (0.48–4.07)	1.05 (0.61–1.81)
PFHxS		
Per doubling	0.87 (0.71–1.06)	0.92 (0.81–1.06)
≥ 90th vs. < 90th percentile (3.5 ng/mL)	1.34 (0.62–2.90)	1.06 (0.60–1.86)
PFDA		
Per doubling	0.93 (0.76–1.13)	1.05 (0.90–1.22)
≥ 90th vs. < 90th percentile (0.5 ng/mL)	1.47 (0.60–3.62)	1.75 (1.00–3.05)
PFNA		
Per doubling	0.92 (0.71–1.20)	1.07 (0.93–1.22)
≥ 90th vs. < 90th percentile (1.8 ng/mL)	1.34 (0.69–2.60)	1.70 (1.13–2.56)

^a All the models were adjusted for age, age square, sex, race/ethnicity, education level, poverty-income ratio, smoking status, body mass index, and noise exposures (occupational, recreational, and firearm noise), and NHANES cycles.

polyhalogenated compounds. Similar to PFAS, these chemicals may disrupt thyroid hormone homeostasis and further lead to loss of outer hair cells (OHCs) and sparing of inner hair cells (IHCs) in the apical turn of cochlea at which lower frequency response locate, leading to low-frequency auditory impairment (Crofton et al., 2000; Powers et al., 2006). Thus, one cannot rule out potential confounding by other chemicals that have been suggested as ototoxic chemicals, although confounding by lead and cadmium is unlikely. Given that people are exposed to a myriad of chemicals daily, it is important to quantify the impact of chemical mixtures in future studies (Wang et al., 2019b, 2019a, 2018). We were also not able to follow the standard for reporting hearing results by the Hearing Committee of the American Academy of Otolaryngology–Head and Neck Surgery (Gurgel et al., 2012), a scattergram relating PTA to word recognition score, because of lack of data on word recognition score.

In summary, the present analysis of a well-defined representative sample of the U.S. adults does not provide strong evidence to support the ototoxicity of PFAS exposure. However, we report non-linear threshold dose-response associations between serum concentrations of PFNA and PFDA and HFHI. Previous research primarily focused on PFOA and PFOS which are the predominant analytical targets detected in the environment. Given that hearing loss is expected to increase from 44 million (~15% of adults) in 2020 to 74 million (~23% of adults) (Goman et al., 2017), our findings still have significant public health implications. Although it is unlikely that our findings are subject to reverse causality, future studies with prospective study designs are needed to confirm concerns related to causal inferences.

CRedit authorship contribution statement

Ning Ding: Conceptualization, Formal analysis, Writing - original draft. **Sung Kyun Park:** Conceptualization, Writing - review & editing, Supervision.

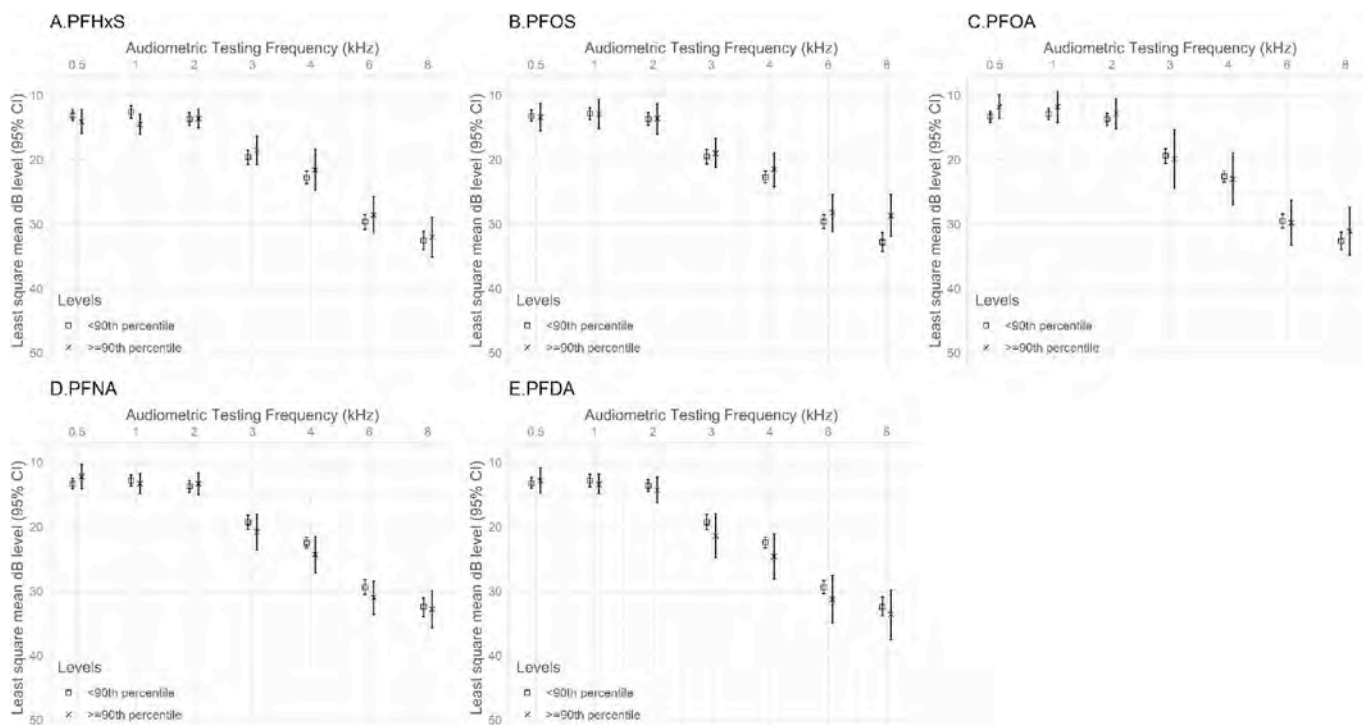


Fig. 2. Survey-weighted least square geometric means and 95% confidence intervals of hearing thresholds in the worse ear at each test frequency by levels of PFAS exposure (≥ 90 th vs. < 90 th percentile) in adults aged 20–69 years. A. PFHxS; B. PFOS; C. PFOA; D. PFNA; E. PFDA. Y axis represents survey-weighted least-square mean decibel levels, and x axis shows audiometric testing frequencies, including 0.5, 1, 2, 3, 4, 6, and 8 kHz. The models were adjusted for age, age squared, sex, race/ethnicity, education, poverty-income ratio, smoking status, body mass index, noise exposure at work, recreational noise exposure, and noise exposure through firearm, and NHANES cycles.

Declaration of competing interest

All authors declare no financial and personal relationships with other people or organizations that could inappropriately influence the work.

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Appendix A. Supplementary data

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