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Associations between serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and thyroid disease; National Health and Nutrition Examination Survey (NHANES): 2007-2010.

By

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Master of Public Health

Epidemiology

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By

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Abstract

Associations between serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and thyroid disease; National Health and Nutrition Examination Survey (NHANES): 2007-2010.

By Evan Coffman

PURPOSE: A prior study found an association between serum concentrations of PFOA/PFOS and prevalent thyroid disease in the U.S. general adult population. The aim of this study was to determine if the association was still persistent, despite an expected decrease in PFOA/PFOS exposure in the same population.
METHODS: This study used a nationally representative sample from the National Health and Nutrition Examination Survey (NHANES) from 2007-2008 and 2009-2010. We had a final sample of n = 3,606, all of whom had measured serum concentrations of PFOA and PFOS, and otherwise met the inclusion criteria. Fully adjusted multivariable logistic regression models were used to calculate odds ratios comparing thyroid disease status across quartiles of serum PFOA/PFOS. We also used two-sample t-tests to compare geometric mean concentrations of PFOA/PFOS from our study population to a past NHANES cohort (2003-2006).
RESULTS: There was a significant decrease in survey-weighted geometric mean serum concentrations of PFOA from 3.96 ng/mL (95% confidence interval (CI): 3.69-4.24ng/mL) in the 2003-2006 population to 3.59 ng/mL (95% CI: 3.43-3.75 ng/mL) in 2007-2010 (p = 0.029). Likewise, geometric mean PFOS levels were significantly lower in the 2007-2010 sample (11.38 ng/mL, 95% CI: 10.52-12.24 ng/mL) than in 2003-2006 (19.01 ng/mL, 95% CI: 18.01-20.01 ng/mL) ($p < 0.001$). The highest quartile of serum PFOA concentration in women was associated with a significant increase in the odds of having a history of thyroid disease compared to the lowest quartile (OR = 2.12, 95% CI: 1.07-4.20; p = 0.031). There were no associations between PFOA exposure and thyroid disease in men, but serum PFOS concentrations were associated with a history of thyroid disease in the highest quartile versus the lowest two (OR = 2.12, 95% CI: 1.09-4.49; p = 0.029).
CONCLUSIONS: Serum concentrations of PFOA and PFOS continue to decrease in the U.S. general adult population. However, while exposure continues to decline, this study provides additional evidence that the highest serum concentrations of PFOA and PFOS are still associated with a history of thyroid disease in U.S. adults.

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Background

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are synthetic compounds with a number of industrial and commercial applications (1). They are two of the most commonly produced perfluorinated chemicals (PFCs) (2), compounds characterized by a particularly strong carbon-fluorine bond (3). This C-F bond creates chemically stable compounds, which contributes to the utility of PFOA and PFOS as surfactants and fire-retardants, among other applications (1). However, as a consequence of this chemical stability, which makes the compounds resistant to degradation, these chemicals remain in the environment indefinitely (4).

Due to the persistence of PFOA and PFOS in the environment, there has been widespread human exposure to these chemicals. It is estimated that a large proportion of the US adult population has measurable serum concentrations of PFOA and PFOS (5). Serum levels of PFC are typically used to monitor exposure, because PFOA and PFOS are lipo-phobic and bind to serum proteins, rather than accumulating in fat tissue (6, 7). Despite its prevalence, sources and mechanisms of human exposure to PFCs are still largely unknown. They have been detected in a number of environmental settings, including ambient air, household dust, and both surface seawater and fresh water (8). While air quality and dust have been considered as potential pathways of exposure, studies have indicated that dietary consumption is likely responsible for the majority of non-occupational exposure (3, 9). Once absorbed, the body is not able to metabolize PFOA (10), and clearance rates for PFCs are generally low (4).

Due to the high prevalence of human exposure to PFCs, there has been increased interest in their potential health effects (3). In animal models toxicology, PFOA and PFOS cause hepatotoxicity, developmental problems, altered immune functions, and exhibit carcinogenic potential (4, 8). Given these findings in animal models, research showing that serum elimination half-life is much longer in humans than other animals raises significant concerns (4). In rats, elimination half-lives have been estimated to be 4-6 days for PFOA and 100 days for PFOS, compared to 21-30 days and 150 days respectively for monkeys, and 3.8 years and 5.4 years for humans (8, 11). The biological foundations leading to the prolonged elimination rates seen in humans are not known (8).

Despite their demonstrated toxicity in animal studies, epidemiological evidence of human health effects is limited, and the results of published studies are conflicting. In a recent review of the epidemiological literature on the health effects of PFOA by Steenland et al., there were consistent associations between increased levels of PFOA and increased plasma levels of cholesterol and uric acid, as well as some increase in liver enzymes (12). Their review, which found most studies to suffer from a lack of sufficient sample size, male-dominant occupational cohorts, and clinically insignificant effects, also found inconsistent associations between PFOA and heart disease, kidney cancer, developmental effects, and diabetes prevalence and mortality. Another review of fluorochemical exposure epidemiology also highlighted the inconsistent results of published studies, but identified a possible association between PFOS exposure and bladder cancer mortality (8).

In addition to the previously discussed toxicological and epidemiological evidence, there is an indication that certain serum-binding chemicals, such as PFCs, may

affect endocrine function (7). Thyroid function is one component of the endocrine system that may be specifically modified by PFOA and PFOS (13). It has been determined that PFCs can compete with thyroid hormones, thyroxine (T4), for binding sites to human thyroid hormone transport proteins, thus altering thyroid hormone levels (14). Of 24 PFCs tested for binding capacity, PFOA and PFOS exhibited the second and third most potent competition for thyroid binding sites (14). This potential for PFOA and PFOS exposure to alter thyroid levels may have key health implications, as thyroid hormones are essential for metabolic, cardiovascular, and reproductive health. There is consistent evidence that PFC exposure is associated with lower T4 levels in rats (8, 15). However, these findings have proven to be mostly null in the limited human studies to date (16-18).

A more recent study by Melzer et. al used the U.S. National Health and Nutrition Examination Survey (NHANES) from 1999-2000, 2003-2004, and 2005-2006 to examine a possible association between PFOA/PFOS exposure and thyroid function in the U.S. general adult population (6). In their analysis, Melzer et al. determined that higher concentrations of serum PFOA and PFOS were associated with self-reported thyroid disease. Specifically, they found that women in the highest quartile of PFOA serum levels were more likely to report thyroid disease than women in the first and second quartile [odds ratio (OR) = 2.12, confidence interval (CI), 1.38-3.65] and men in the highest quartile of PFOS serum levels were more likely to report thyroid disease than men in the first and second quartile (OR = 2.68, CI, 1.03-6.98). Additionally, they found a near significant association between men in the highest quartile of PFOA serum levels and reported thyroid disease (OR = 2.12, CI, 0.93-4.82), but no association between

PFOS serum levels in women and self-reported thyroid disease. These findings are important because they provide possible evidence of PFOA- and PFOS-induced disruption of thyroid function in a large population sample. This provided more information on the effect of background levels of PFOA/PFOS in contrast to the more plentiful research on occupational exposure.

In light of their findings, this paper attempts to replicate their original analysis using newer cohorts of NHANES data (2007-2008 and 2009-2010), to determine whether these effects remain apparent in a more recent sample. This is a critical next step understanding the potential association between PFC exposure and thyroid function using contemporary information in view of raised awareness and recent efforts to curb the use of PFOA and PFOS chemicals. These efforts have been led by the complete phase-out of all PFOS and PFOA compounds by 3M, the leading producer of PFOS in the United States, in 2002 (4). Global annual production of PFOS has fallen from 3500 metric tons in 2000 to 175 metric tons by 2003 (8), with evidence of a measurable reduction in serum concentrations of PFOA and PFOS in the US general population (5, 19). In this study, I expect to see these two trends continue. I hypothesize that there will be a continued reduction in serum levels of PFOA/PFOS compared to past NHANES cohorts, consistent with other recent findings. Further, despite these potential decreases, I anticipate that, because of the long elimination half-lives of PFOA and PFOS resulting in prolonged exposure, significant associations between PFOA/PFOS levels and self-reported thyroid disease will persist.

Methods

Study Design. A cross-sectional study was conducted using data from two independent cycles of NHANES (2007-2008 and 2009-2010). NHANES uses a complex, multistage, unequal probability of selection, cluster design in order to provide a nationally representative sample of the non-institutionalized U.S. civilian population. The survey is comprised of two segments: (1) an interview, which collects information on demographics, socioeconomic status, dietary habits, and medical history; and (2) an examination section, involving dental, medical, and physiological evaluation and laboratory testing. The NHANES protocol has been approved by the National Center for Health Statistics Institutional Review Board, and written informed consent was obtained from all participants.

Study Population. The target population for the current analysis is adults over 20 years of age who completed the laboratory component of the survey, and answered questions about their history of thyroid disease. These selection criteria are identical to those of the study by Melzer et al. (6), in order to assure comparability of the populations. Serum concentrations of PFOA and PFOS were available for n = 3,612 subjects who were over 20 years old. Of the individuals with measured PFC concentrations, n = 6 were excluded because they did not answer questions about their history of thyroid disease, making the final sample size for this analysis n = 3,606.

Laboratory Assessment. Serum levels of PFCs were measured in a subsample consisting of one-third of all persons 12 years of age and older in each respective NHANES wave. The subsamples were nationally representative, and appropriate sample weights were provided for proper statistical estimation. PFOA and PFOS serum levels were detected

using solid phase extraction coupled to High Performance Liquid Chromatography-Turbo Ion Spray ionization-tandem Mass Spectrometry (online SPE-HPLC-TIS-MS/MS) (20), as performed by the Organic Analytical Toxicology Branch at the National Center for Environmental Health. The lower limits of detection for PFOA and PFOS were 0.1 ng/mL and 0.2 ng/mL, respectively. Less than 0.5% of all eligible participants had PFOA or PFOS serum concentrations below the limits of detection. Participants with PFOA and/or PFOS levels below the limits of detection were assigned a value equal to the limit of detection divided by the square root of two.

Thyroid Disease. NHANES respondents were asked questions about a number of physician-diagnosed diseases. For this analysis, we were particularly interested in thyroid disease, for which we used two definitions for the analysis. First, we defined history of thyroid disease as adult respondents who reported being told by a doctor or health professional that they had a thyroid problem at some point in their lives. We alternatively defined current thyroid disease as respondents who reported an ongoing thyroid problem and who were taking any thyroid-related medications. Thyroid-related medications included levothyroxine, liothyronine, "thyroid desiccated", and "thyroid drugs unspecified" for hypothyroidism and propylthiouracil and methimazole for hyperthyroidism (6).

Statistical Analyses. Multivariate logistic regression was used to calculate estimated odds ratios (ORs) to measure the relationship between thyroid disease and serum PFOA and PFOS levels. We used separate models for comparing PFOA and PFOS levels of those with a history of thyroid disease to those without and those who currently have thyroid disease to those who do not. As with many environmental contaminants, serum

levels of PFOA and PFOS are heavily skewed, and thus exposure was measured in the model by population-weighted quartiles. As an alternative to the population-weighted quartiles, we split exposure levels into four groups based on the population-weighted quartile PFOA and PFOS cut-points derived from 1999-2000, 2003-2004, and 2005-2006 NHANES cycles. This would allow for a direct comparison to the associations seen in the study by Melzer et al. Also similar to Melzer et al., we used sex-specific models because prevalence of thyroid disease is considerably higher in women.

To control for potential confounding factors, the models were adjusted for age, sex, race/ethnicity, education, body mass index (BMI), cigarette smoking, alcohol use, and NHANES survey year. Subjects were divided into three groups based on age: 20-49 years old, 50-69 years old, and 70+ years old; race/ethnicity was classified as: Mexican American, other Hispanic, non-Hispanic black, non-Hispanic white, and other race; education was categorized as: less than a high school diploma, high school graduate (including GED), education beyond high school, and unknown education; BMI was separated using CDC standard weight categories: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (>30 kg/m^2); for cigarette smoking, subjects were classified as: non-smokers, former smokers, occasional smokers, everyday smokers, and unknown smoking status; and alcohol use was categorized by average drinks per day (based on alcohol use over the 12 months leading up to the survey) from: 1 to 5+ drinks, with groups for non-drinkers and those whose alcohol use was unknown. Because of the small number of respondents whose education, smoking status, and alcohol use was unknown (n=9, n=1, and n=5, respectively), the unknowns for each category were changed to “missing” values to help with the

convergence of the logistic regression model. These changes had little or no effect on the ORs estimating the association between thyroid disease and PFOA/PFOS.

Because of the wide categorization of age groups determined by Melzer et al., we were concerned about the possibility of residual confounding within the large age strata. In order to assess this potential for residual confounding, we re-analyzed the regression models using narrower age categorizations, grouping subjects by ten-year intervals from 20 to 70 years old, and maintaining one group for those participants who were older than 70.

In addition to the regression analysis, we used two-sample t-tests to determine differences in geometric mean concentrations of PFOA and PFOS between 2003-2006 and 2007-2010, by pooling NHANES 2003-2004 and 2005-2006 waves; and 2007-2008 and 2009-2010 waves. Geometric means were used to account for the skewedness of PFOA/PFOS concentrations, and survey-weights were used to determine standard errors and degrees of freedom for the t-tests. Additionally, geometric mean comparisons were stratified by age, sex, and race/ethnicity. While we would have ideally preferred to compare the PFC levels in our study population directly to those reported by Melzer et al., this would not have been a meaningful comparison. Combining NHANES survey cycles provides a representation of the population at the midpoint of the combined survey years. Since the study by Meltzer and associates was carried out in non-adjacent years, the point estimate would not be representative of an actual time period. Therefore, we instead compared PFOA/PFOS serum levels from 2003-2006 to 2007-2010, in order to provide a more meaningful estimate of potential changes of levels with time.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, N.C.) and SAS-callable SUDAAN version 10 (Research Triangle Institute, Research Triangle Park, N.C.). SUDAAN was used to calculate survey-weighted variance estimates, which account for unequal probability of selection and the intentional oversampling of demographic groups as a part of the NHANES complex multistage cluster design.

Results

General characteristics of the study population. The final study population was comprised of n = 3,606 U.S. adults aged 20 years or older, who met the inclusion criteria, as previously defined. The sample included n = 1,735 males and n = 1,871 females, and consisted of n = 1,739 participants from the 2007-2008 NHANES cohort and n = 1,867 participants from the 2009-2010 NHANES cohort.

Serum PFOA/PFOS levels. In participants with levels greater than the limits of detection, serum PFOA concentrations in women ranged from 0.1 ng/mL to 23.9 ng/mL, whereas in men the range was from 0.1 ng/mL to 104.0 ng/mL. The range of serum PFOS exposure was 0.1 ng/mL to 178.0 ng/mL in women, and 0.1 ng/mL to 281.0 mg/mL in men. Men had significantly higher survey-weighted geometric mean serum concentrations of PFOA (4.22 ng/mL, 95% confidence interval (CI): 4.01-4.22 ng/mL) and PFOS (14.40 ng/mL, 95% CI: 13.27-15.54 ng/mL) than women (3.08 ng/mL, 95% CI: 2.91-3.25 ng/mL; 9.10 ng/mL, 95% CI: 8.36-9.84 ng/mL) (Table 1). There were also significant differences in PFOA and PFOS levels between ethnic groups, with generally higher levels seen in non-Hispanic whites and lower levels in Mexican Americans. In addition, survey-weighted geometric mean serum PFOS levels increased with age.

Thyroid disease. In the study population, n = 274 women reported a history of thyroid disease, compared to just n = 64 men (Table 2). The unadjusted survey-weighted prevalence of thyroid disease history was significantly higher among women (15.05%, 95% CI: 13.16-16.85%) than men (3.79%, 95% CI: 2.71-4.87%). These numbers were lower for those with current thyroid disease who were also taking thyroid-related medication (women: n = 177, 10.42%; men: n = 43, 2.39%).

Thyroid disease prevalence and PFOA/PFOS exposure. There was a significantly higher unadjusted survey-weighted prevalence of thyroid disease history in women in the highest PFOA exposure quartile (Q4: > 4.7 ng/mL) (21.51%, 95% CI: 16.03-27.00%) than those in the lowest exposure quartile (Q1: ≤ 2.1 ng/mL) (8.06%, 95% CI: 4.83-11.29%). This relationship was also observed for PFOS: Q4 (> 15.1 ng/mL) (20.71%, 95% CI: 15.70-25.72%) compared to the Q1 (≤ 5.5 ng/mL) (10.85%, 95% CI: 7.49-14.21%). These prevalence trends remained significant when measuring current thyroid disease in women across exposure quartiles, however there were no significant differences in comparing the prevalence of either measure of thyroid disease in the highest and lowest quartiles of PFOA and PFOS serum levels in men.

PFOA/PFOS exposure trends. Two-sample t-tests showed that serum levels of PFOA and PFOS from our sample population were significantly lower than the two previous NHANES waves (Table 3). The geometric mean serum PFOS concentration in pooled NHANES 2007-2008 and 2009-2010 waves (11.38 ng/mL 95% CI: 10.52-12.24 ng/mL) was significantly lower than in pooled NHANES 2003-2004 and 2005-2006 waves (19.01 ng/mL 95% CI: 18.01-20.01 ng/mL) ($p < 0.001$). PFOS levels were lower in the later NHANES waves for both males and females, and across all age and race/ethnicity groups ($p < 0.001$).

Similarly, combined NHANES 2007-2008 and 2009-2010 waves had significantly lower geometric-mean serum PFOA levels (3.96 ng/mL, 95% CI: 3.69-4.24) than in combined NHANES 2003-2004 and 2005-2006 waves (3.59 ng/mL, 95% CI: 3.43-3.75) ($p = 0.029$). PFOA levels were lower in the later NHANES waves for males

and females, non-Hispanic Whites, and 20 to 49 year-olds ($p < 0.05$), and approached significance in 50 to 69 year olds ($p = 0.055$).

Association between PFOA and thyroid disease. Despite the decrease in population PFOA and PFOS serum levels, we still found significant associations between PFOA/PFOS and thyroid disease. As seen in the comparison of unadjusted survey-weighted prevalences of thyroid disease across PFOA exposure quartiles in women, unadjusted logistic regression models showed significant associations between PFOA exposure and history of thyroid disease in women. Notably, in women, the crude odds ratios (ORs) comparing thyroid disease history across PFOA exposure groups demonstrates a near dose-response type relationship, with increasing PFOA exposure corresponding to increasing odds of thyroid disease history. The unadjusted OR comparing thyroid disease history in women in PFOA Q2 vs. Q1 was 1.95 (95% CI: 1.11-3.44; $p = 0.022$), Q3 vs. Q1 was 2.07 (95% CI: 1.27-3.38; $p = 0.005$), and Q4 vs. Q1 was 3.13 (95% CI: 1.93-5.05; $p < 0.001$). Additionally, there was a near significant difference between Q4 and Q2 (OR = 1.60, 95% CI: 0.93-2.74; $p = 0.085$), and a significant difference between Q4 and Q3 (OR = 1.51, 95% CI: 1.01-2.27; $p = 0.047$).

The crude associations between thyroid disease and PFOA exposure were not as stark in the fully adjusted logistic regression models, but some associations were still present (Table 4). As in the crude models, there were no significant associations between PFOA exposure and thyroid disease (either current disease or history of disease) in men. Yet, we found a significant association between PFOA exposure and history of thyroid in women when comparing Q4 to Q1 (OR = 2.12, 95% CI: 1.07-4.20; $p = 0.031$), as well as a near significant association in women with current thyroid disease (OR = 2.54, 95% CI:

0.99-6.56; p = 0.053). Comparing the highest and lowest exposure groups using the quartiles determined by Melzer et al. for their study population, there was a significant association between PFOA exposure and current thyroid disease in women (OR = 2.45, 95% CI: 1.16-5.20; p = 0.021), and a near significant association in women with a history of thyroid disease (OR = 1.72, 95% CI: 0.92-3.21; p = 0.085).

In addition to the associations seen using a categorized PFOA exposure variable, we analyzed sex-specific fully adjusted logistic regression models using a continuous log-transformed PFOA predictor variable. Increased log-transformed serum PFOA levels were also associated with higher odds of a history of thyroid disease in women (regression coefficient per 1 ln unit [β]=0.39, 95% CI: 0.05-0.73; p = 0.028), but not in men.

Association between PFOS and thyroid disease. The crude OR comparing history of thyroid disease in women and PFOS Q4 vs. Q1 was 2.15 (95% CI: 1.31-3.52, p = 0.004). However, in the fully adjusted logistic regression model, there was no significant association between PFOS and history of thyroid disease or current thyroid disease in women. In contrast, there was a significant association found between history of thyroid disease in men and PFOS exposure when comparing Q4 to Q1 and Q2 (OR = 2.12, 95% CI: 1.09-4.49; p = 0.029). However, the continuous models using log-transformed serum PFOS levels were not associated with higher odds of thyroid disease in men or women.

Residual Confounding Assessment. Due to the wide categorization of age groups, we were concerned about the potential for residual confounding. In order to control for this potential confounding, we adjusted the models using narrower age categorizations. These new groupings did not result in any meaningful changes in the ORs, and only

slightly wider CIs, estimating the association between thyroid disease and PFOA/PFOS. For example, using the broad age groups, the OR comparing thyroid disease history in women in Q4 vs. Q1 was 2.12 (95% CI: 1.07-4.20), compared to 2.13 (95% CI: 1.05-4.30) when the model was adjusted using smaller age groups. The same quartile comparisons of PFOA and history of thyroid disease in men yielded the following ORs: 0.82 (95% CI: 0.32-2.13) for the models adjusted using larger age groups, and 0.86 (95% CI: 0.33-2.21) for the more narrow age categorizations.

Discussion

Meltzer and associates found significant associations between serum PFOA and PFOS concentrations and thyroid disease in a previous analysis of NHANES. During the span of their study, there was a self-imposed phase out of PFCs by a major US manufacturer (4), and subsequent reduction in global PFOA and PFOS production (8), with observed decreases in human exposure (5). Thus, we hypothesized that the declining exposure trend would continue to be reflected in the US population by reduced PFOA/PFOS serum concentrations, but due to the long serum half-lives of the chemicals (8) we expected to see continued associations with thyroid disease. Accordingly, the objectives of our study were two-fold: (1) to examine trends of PFOA and PFOS exposure in the U.S. general adult population, using the NHANES datasets, and, (2) in light of current trends, reevaluate the associations between PFOA/PFOS and thyroid disease reported in a previous NHANES study by Melzer et al.

Consistent with prior studies (5), we saw a significant decrease in PFOS levels from 2003-2006 to 2007-2010, with large reductions in serum PFOS concentrations across all measured demographic groups. Likewise, we found a significant drop in PFOA levels in the total population over this same time. While the decreases in PFOA levels were not seen across all race and age groups, this was likely attributable to the observed low PFOA levels in some of these groups compared to the population average from the earlier 2003-2006 samples. Regardless, the results show a marked decline in PFOA and PFOS levels in the U.S. general population.

Despite the drop in PFOA/PFOS exposure over time, we found a persistent association between PFOA levels and a history of thyroid disease in women, and an

association between PFOS levels and a history of thyroid disease in men. Our findings were consistent with those of Melzer et al., who found that PFOA levels in women and PFOS levels in men were associated with current thyroid disease. While Melzer et al. found a near significant association between thyroid disease and PFOA in men, we saw no evidence of this association. This discrepancy may have been due to the comparably lower number of men with thyroid disease in our study. To the best of our knowledge, the mechanisms of sex-specific responses to PFOA and PFOS are unknown. However, there have been multiple studies that highlight the sex related differences in response to exposure. There have been other gender-specific associations with chronic conditions (22), sex-related neurobehavioral alterations in prenatally exposed mice (23), and specific to our study, interactions between gender and PFOA/PFOS on T3 uptake, TSH, and thyroxine (24).

In further comparing our study population to Melzer et al.'s, we applied the serum concentration levels that marked the quartile exposure levels of PFOA and PFOA from 1999-2000, 2003-2004, and 2005-2006 NHANES waves to our sample population and re-analyzed the data. Because we expected lower levels of PFOA and PFOS exposure in our study population from the more recent NHANES wave, we used these alternative categorizations to see if the associations were potentially only existent, or stronger, at a particularly higher level of exposure. Using these cutoffs, we only saw an association between PFOA exposure and treated thyroid disease in women. We did not see any evidence of higher odds in the most extreme levels of exposure, compared to the highest quartile levels of exposure from our study population, which likely indicates that there is

not a dose-response association between PFOA and thyroid disease, as the crude results may have suggested.

Strengths and Limitations. There are a number of limitations that impact the strength of the conclusions that can be drawn from this study. As with all cross-sectional studies, there is no way of determining a temporal link between the exposures and the outcome. Therefore, we are unable to infer causality in the association of PFOA and PFOS exposure and thyroid disease. Because we are unable to discern the causal direction, there is a possibility of reverse causality, whereby thyroid disease could be related to reduced excretion or altered metabolism of PFCs. In relation to the issue of causality, another limitation is that the PFC serum measurements in this study did not take place in the relevant exposure window, because the disease outcome had already occurred. Therefore, we can only use PFOA and PFOS measurements in our study as a proxy for exposure in the relevant window, which is unknown. While we do not know how good of a proxy these measurements are, the long serum half-life of PFCs, along with their temporal reduction in the environment, result in a relatively larger percentage of a person's serum levels being the result of their historic exposures.

Additionally, due to the nature the survey, many of the variables we used were self-reported, and not verified. Although we would not expect the reporting of thyroid disease to be directly influenced by exposure status, which was likely unknown to the participants, it is possible that thyroid disease was under- or over-reported by some factor related to exposure (e.g., age) and could have induced bias in either direction. Our study was also limited by a small number of reported cases of disease. The small sample-size, in addition to controlling for a number of potential confounders, resulted in large

confidence intervals. This was especially true in analyses using treated thyroid disease, where the number of subjects was even smaller and the precision was lower. Finally, using serum concentrations of PFCs is an imperfect measure of exposure, because it does not account for the duration that a person has been exposed.

Despite the limitations of our analyses, there are also a number of strengths that should be highlighted. NHANES uses a nationally representative sampling method, such that our results are generalizable to the U.S. general population. It provides a series of detailed characterizations of the U.S. population over time, allowing for historical comparisons with consistent approaches for data collection. A publically available dataset containing reliable PFOA and PFOS measurements in a reasonably sized cohort is unavailable elsewhere. Our results can also be compared to other directly related studies, with consistent results (5, 6, 21).

Future Directions. In the context of previous work, our study provides some additional evidence of an association between PFC serum concentrations and thyroid disease in the U.S. general adult population. Given these persistent associations, despite a decrease in overall PFOA and PFOS levels, we speculate that high serum concentrations might be an indicator of prolonged and high levels of past exposure. Thus, it might be useful in future studies to examine the relationship between extended previous exposure and current levels of PFOA and PFOS, and correlate these with thyroid disease status. Longitudinal studies on PFOA/PFOS exposure and thyroid disease onset could provide additional detail about the nature of this relationship. Furthermore, despite the emerging evidence that PFOA exposure is associated with thyroid disease (5, 6, 21), previous research has indicated a lack of association between serum PFOA concentrations and levels of thyroid

hormone in humans (16-18, 21), in most but not all studies (24). This raises questions about the nature of the biological mechanisms of PFOA/PFOS that affect thyroid function. The apparent differences in the impact of PFOA and PFOS in males and females are also unexplained and would be an interesting area for future work.

Conclusions. Serum concentrations of PFOA and PFOS continue to decrease in the U.S. general adult population. However, while exposure continues to decline, this study provides some additional evidence that the highest serum concentrations of PFOA and PFOS are still associated with a history of thyroid disease in U.S. adults.

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Tables

Table 1. Demographic group survey-weighted geometric mean serum concentrations (95% CIs) of PFOA and PFOS.

	Males			Females		
Groups	**n (% within group[1])**	**PFOA**	**PFOS**	**n (% within group[1])**	**PFOA**	**PFOS**
Overall	1,735 (100)	4.22 (4.01-4.42)	14.40 (13.27-15.54)	1,871 (100)	3.08 (2.91-3.25)	9.10 (8.36-9.84)
Age (Years)						
20-49	844 (58.8)	4.34 (4.08-4.59)	13.25 (12.07-14.43)	933 (56.0)	2.65 (2.48-2.83)	7.16 (6.43-7.89)
50-69	573 (31.0)	4.05 (3.79-4.32)	15.51 (14.01-17.01)	613 (31.5)	3.75 (3.44-4.06)	11.67 (10.47-12.88)
70+	318 (10.2)	4.04 (3.56-4.52)	18.58 (15.83-21.33)	325 (12.5)	3.68 (3.42-3.93)	14.26 (12.92-15.60)
Ethnicity						
Mexican American	300 (9.4)	3.47 (3.16-3.77)	11.25 (10.21-12.29)	351 (8.0)	2.24 (2.00-2.48)	6.10 (5.31-6.90)
Other Hispanic	176 (4.9)	3.42 (2.93-3.90)	9.63 (7.92-11.35)	213 (4.9)	2.40 (2.10-2.70)	6.23 (5.25-7.22)
Non-Hispanic White	858 (69.3)	4.48 (4.22-4.74)	15.22 (13.85-16.60)	876 (68.8)	3.34 (3.13-3.55)	9.54 (8.67-10.41)
Non-Hispanic Black	314 (9.7)	4.11 (3.58-4.64)	16.13 (13.53-18.73)	337 (11.4)	2.74 (2.54-2.95)	9.76 (8.28-11.23)
Other	87 (6.7)	3.56 (2.90-4.21)	13.14 (9.40-16.87)	94 (6.9)	2.93 (2.37-3.49)	10.55 (7.71-13.38)
Education						
< High School	527 (20.0)	3.78 (3.44-4.11)	13.57 (12.31-14.83)	549 (19.1)	2.77 (2.54-3.01)	8.26 (7.48-9.05)
High School Graduate	397 (23.1)	4.38 (3.94-4.82)	15.48 (13.57-17.39)	410 (21.5)	3.33 (3.01-3.66)	10.64 (9.10-12.18)
> High School	808 (56.7)	4.31 (4.08-4.45)	14.27 (12.92-15.62)	906 (59.3)	3.10 (2.91-3.29)	8.87 (7.94-9.81)
Unknown	3 (0.2)	5.86 (5.08-6.64)	20.29 (12.84-27.74)	6 (0.1)	2.87 (1.26-4.48)	7.35 (0.10-14.95)
BMI (kg/m^2)						
Underweight (0-18.5)	39 (1.9)	3.47 (2.23-4.70)	11.83 (7.70-15.95)	56 (3.6)	2.54 (1.67-3.42)	7.67 (4.26-11.09)
Normal (18.5-25)	443 (24.8)	4.19 (3.82-4.57)	14.12 (12.41-15.82)	523 (32.8)	3.05 (2.83-3.27)	9.44 (8.41-10.47)
Overweight (25-30)	665 (39.4)	4.32 (4.09-4.56)	14.47 (13.17-15.76)	542 (28.4)	3.11 (2.86-3.37)	9.04 (7.97-10.11)
Obese (30+)	588 (33.9)	4.16 (3.88-4.43)	14.71 (13.17-16.25)	750 (35.2)	3.15 (2.96-3.34)	9.00 (8.21-9.79)
Smoking Status						
Non-Smoker	766 (47.4)	4.23 (3.98-4.49)	14.79 (13.64-15.93)	1,161 (62.0)	2.96 (2.77-3.16)	9.22 (8.28-10.16)
Former Smoker	539 (28.3)	4.24 (3.97-4.51)	15.48 (13.61-17.35)	360 (18.9)	3.21 (2.93-3.49)	8.88 (7.92-9.84)
Some Days	84 (3.8)	3.64 (2.76-4.52)	10.62 (6.78-14.45)	51 (2.5)	3.09 (2.40-3.78)	8.20 (6.22-10.19)
Every Day	355 (20.5)	4.25 (3.82-4.68)	12.98 (11.25-14.71)	298 (16.6)	3.40 (3.17-3.64)	9.05 (8.20-9.89)
Unknown	1 (0.0)					
Average Drinks Per Day/ Last 12 Months						
Non-Drinker	256 (17.0)	3.89 (3.52-4.26)	13.95 (11.83-16.07)	669 (35.4)	2.88 (2.64-3.12)	9.54 (8.64-10.45)
1	257 (19.1)	4.27 (3.94-4.59)	14.66 (12.83-16.49)	337 (27.6)	3.36 (3.14-3.58)	9.35 (8.43-10.27)
2	272 (22.9)	4.23 (3.83-4.64)	15.25 (12.48-18.01)	259 (19.5)	3.44 (3.09-3.79)	10.06 (8.40-11.71)
3	172 (13.2)	4.52 (3.97-5.08)	15.52 (12.89-18.16)	115 (8.7)	2.97 (2.53-3.41)	7.36 (6.09-8.62)
4	95 (6.8)	4.44 (3.68-5.20)	13.66 (11.37-15.95)	53 (3.5)	2.90 (2.20-3.60)	7.96 (6.79-9.12)
5+	288 (20.9)	4.35 (3.93-4.76)	13.22 (11.81-14.63)	75 (5.2)	3.05 (2.42-3.69)	7.07 (5.61-8.54)
Unknown	2 (0.1)	1.99 (0.64-3.34)	11.26 (5.32-17.20)	3 (0.1)	2.51 (0.10-5.01)	23.18 (0.10-66.04)

[1]Percentage within group is survey-weighted.

Table 2. Sex-Specific, population-based serum PFOA/PFOS exposure quartiles and thyroid disease prevalence.

		Thyroid Disease Ever			Current Thyroid Disease With Medication		
	Analyte Range (ng/mL)	n (Case/Total)	Unweighted Prevalence (%)	Weighted Prevalence (% (95% CI))	n (Case/Total)	Unweighted Prevalence (%)	Weighted Prevalence (% (95% CI))
Female							
PFOA							
All	0.1-23.9	274/1871	14.64	15.05 (13.16-16.95)	177/1871	9.46	10.42 (8.74-12.10)
Q1	0.1-2.1	41/492	8.33	8.06 (4.83-11.29)	21/492	4.27	4.72 (2.01-7.44)
Q2	2.1-3.2	70/487	14.37	14.63 (10.43-18.83)	46/487	9.45	9.36 (5.72-13.03)
Q3	3.2-4.7	72/452	15.93	15.37 (12.26-18.48)	44/452	9.73	10.68 (7.37-14.00)
Q4	4.7-23.9	91/440	20.68	21.51 (16.03-27.00)	66/440	15.00	16.40 (11.81-20.99)
PFOS							
All	0.1-178.0	274/1871	14.64	15.05 (13.16-16.95)	177/1871	9.46	10.42 (8.74-12.10)
Q1	0.1-5.5	54/512	10.55	10.85 (7.49-14.21)	30/512	5.86	6.63 (4.13-9.13)
Q2	5.5-9.3	63/430	14.65	15.41 (10.34-20.49)	39/430	9.07	10.60 (5.96-15.24)
Q3	9.3-15.1	62/443	14.00	13.21 (9.20-17.23)	43/443	9.71	9.58 (5.93-13.22)
Q4	15.1-178.0	95/486	19.55	20.71 (15.70-25.72)	65/486	13.37	14.83 (10.30-19.36)
Male							
PFOA							
All	0.1-104.0	64/1735	3.69	3.79 (2.71-4.87)	43/1735	2.48	2.39 (1.64-3.14)
Q1	0.1-3.0	20/495	4.04	3.27 (1.19-5.35)	16/495	3.23	2.90 (0.88-4.93)
Q2	3.0-4.3	20/435	4.60	5.11 (2.27-7.95)	14/435	3.22	3.10 (0.80-5.40)
Q3	4.3-5.9	12/411	2.92	4.24 (2.05-6.44)	7/411	1.70	2.37 (0.86-3.88)
Q4	5.9-104.0	12/394	3.05	2.52 (1.18-3.86)	6/394	1.52	1.19 (0.73-1.66)
PFOS							
All	0.1-281.0	64/1735	3.69	3.79 (2.71-4.87)	43/1735	2.48	2.39 (1.64-3.14)
Q1	0.1-9.7	17/461	3.69	3.26 (1.34-5.18)	14/461	3.04	3.00 (0.94-5.06)
Q2	9.7-14.6	13/397	3.27	2.00 (0.50-3.50)	9/397	2.27	1.41 (0.19-2.64)
Q3	14.6-21.7	12/407	2.95	3.96 (1.07-6.85)	7/407	1.72	1.99 (0.01-3.97)
Q4	21.7-281.0	22/470	4.68	5.91 (3.66-8.17)	13/470	2.77	3.14 (2.26-4.02)

Table 3. Comparison of geometric mean concentrations (95% confidence intervals) of serum PFOA and PFOS from 2003-2006 and 2007-2010.

Demographic Group	2003-2006	2007-2010	p-Value[1]
PFOA			
All	3.96 (3.69-4.24)	3.59 (3.43-3.75)	0.029*
20-49 years	3.81 (3.55-4.08)	3.39 (3.19-3.59)	0.016*
50-69 years	4.31 (3.93-4.69)	3.89 (3.72-4.07)	0.055
70+ years	3.94 (3.47-4.42)	3.83 (3.52-4.14)	0.692
Male	4.65 (4.33-4.96)	4.22 (4.01-4.42)	0.024*
Female	3.41 (3.14-3.69)	3.08 (2.91-3.25)	0.039*
Mexican American	2.78 (2.53-3.03)	2.82 (2.59-3.05)	0.809
Non-Hispanic Black	3.28 (2.85-3.71)	3.29 (3.00-3.57)	0.969
Non-Hispanic White	4.26 (3.97-4.56)	3.85 (3.67-4.04)	0.020*
PFOS			
All	19.01 (18.01-20.01)	11.38 (10.52-12.24)	<0.001*
20-49 years	16.90 (15.85-17.95)	9.73 (8.85-10.62)	<0.001*
50-69 years	22.53 (20.99-24.07)	13.39 (12.37-14.40)	<0.001*
70+ years	22.68 (20.75-24.61)	16.01 (14.55-17.47)	<0.001*
Male	22.39 (21.06-23.72)	14.40 (13.27-15.54)	<0.001*
Female	16.29 (15.30-17.28)	9.10 (8.36-9.84)	<0.001*
Mexican American	12.80 (11.50-14.10)	8.42 (7.62-9.22)	<0.001*
Non-Hispanic Black	20.62 (18.30-22.94)	12.20 (10.49-13.91)	<0.001*
Non-Hispanic White	19.82 (18.80-20.84)	11.99 (10.99-12.98)	<0.001*

[1]p-Value for two-sample t-test for geometric mean differences between survey time period.
* $p < 0.05$.

Table 4. Sex-specific, survey-weighted associations between serum PFOA/PFOS concentration quartiles and thyroid disease in fully adjusted logistic regression models[1].

	PFOA		PFOS	
Group/Quartile	**Current Quartiles[2]**	**Past Quartiles[3]**	**Current Quartiles[2]**	**Past Quartiles[3]**
Females				
Thyroid Disease - Ever				
Q1 (Reference)	1	1	1	1
Q2	1.81 (0.88-3.71), *p*=0.104	1.53 (0.89-2.63), *p*=0.122	1.44 (0.77-2.71), *p*=0.246	1.41 (0.76-2.60), *p*=0.266
Q3	1.34 (0.68-2.65), *p*=0.383	1.23 (0.59-2.56), *p*=0.570	0.90 (0.52-1.57), *p*=0.670	0.74 (0.34-1.72), *p*=0.501
Q4	2.12 (1.07-4.20), *p*=0.031*	1.72 (0.92-3.21), *p*=0.085	1.25 (0.59-2.63), *p*=0.555	1.44 (0.59-3.51), *p*=0.414
Q4 vs. Q1 and Q2	1.44 (0.80-2.58), *p*=0.215	1.37 (0.77-2.42), *p*=0.270	1.01 (0.52-1.95), *p*=0.974	1.28 (0.57-2.83), *p*=0.539
Thyroid Disease With Current Medication				
Q1 (Reference)	1	1	1	1
Q2	1.73 (0.69-4.36), *p*=0.235	2.18 (1.17-4.03), *p*=0.015*	1.65 (0.73-3.72), *p*=0.219	1.35 (0.68-2.69), *p*=0.385
Q3	1.35 (0.48-3.81), *p*=0.556	1.76 (0.80-3.90), *p*=0.156	1.11 (0.56-2.20), *p*=0.769	0.70 (0.25-1.92), *p*=0.476
Q4	2.54 (0.99-6.56), *p*=0.053	2.45 (1.16-5.20), *p*=0.021*	1.59 (0.64-3.93), *p*=0.308	1.98 (0.73-5.35), *p*=0.174
Q4 vs. Q1 and Q2	1.77 (0.91-3.43), *p*=0.091	1.56 (0.76-3.20), *p*=0.216	1.19 (0.53-2.67), *p*=0.673	1.78 (0.73-4.31), p=0.195
Males				
Thyroid Disease - Ever				
Q1 (Reference)	1	1	1	1
Q2	0.86 (0.32-2.32), *p*=0.758	1.06 (0.37-3.02), *p*=0.910	0.40 (0.11-1.51), *p*=0.169	1.02 (0.40-2.58), *p*=0.964
Q3	1.41 (0.54-3.65), *p*=0.469	1.47 (0.52-4.19), *p*=0.456	0.76 (0.22-2.65), *p*=0.658	2.71 (0.93-7.86), *p*=0.066
Q4	0.82 (0.32-2.13), *p*=0.672	0.71 (0.26-1.90), *p*=0.479	1.45 (0.53-3.93), *p*=0.453	1.44 (0.66-3.10), *p*=0.347
Q4 vs. Q1 and Q2	0.89 (0.41-1.92), *p*=0.759	0.69 (0.30-1.57), *p*=0.360	2.21 (1.09-4.49), *p*=0.029*	1.43 (0.68-3.01), p=0.340
Thyroid Disease With Current Medication				
Q1 (Reference)	1	1	1	1
Q2	0.66 (0.19-2.33), *p*=0.508	0.72 (0.22-2.35), *p*=0.577	0.24 (0.06-0.96), *p*=0.044*	0.72 (0.18-2.84), *p*=0.633
Q3	1.06 (0.31-3.61), *p*=0.918	1.35 (0.42-4.37), *p*=0.608	0.64 (0.15-2.71), *p*=0.538	1.05 (0.20-5.44), *p*=0.949
Q4	0.54 (0.20-1.44), *p*=0.208	0.49 (0.18-1.29), *p*=0.143	0.86 (0.28-2.65), *p*=0.794	1.57 (0.64-3.81), *p*=0.311
Q4 vs. Q1 and Q2	0.67 (0.29-1.57), *p*=0.343	0.56 (0.25-1.26), *p*=0.157	1.56 (0.70-3.48), *p*=0.270	1.69 (0.70-4.03), *p*=0.232

[1]Models are adjusted for age, survey-year, ethnicity, education, BMI, smoking status, and alcohol use.

[2]Survey-Weighted Quartiles from 2007-08 and 2009-10 NHANES waves.

[3]Survey-Weighted Quartiles from 1999-2000, 2003-2004 and 2005-06 NHANES samples.

* $p < 0.05$.