Perfluorooctanoic Acid Exposure and Thyroid Disease in Community and Worker Cohorts

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Background: Perfluorooctanoic acid (PFOA) was released from a mid-Ohio River Valley chemical plant, exposing the surrounding community to PFOA for >50 years, primarily through drinking water. Toxicological studies and some previous human studies have suggested that PFOA can disrupt thyroid homeostasis. We examined the association between PFOA and thyroid disease among community members and plant workers.

Methods: Participants completed health surveys during 2008–2011. Yearly serum PFOA concentrations were estimated for each participant starting at birth or in 1952, whichever came later. We used Cox proportional hazard models, stratified by birth year, to assess adult thyroid disease hazard in relation to time-varying yearly or cumulative (sum of yearly estimates) estimated PFOA serum concentration, controlling for sex, race, education, smoking, and alcohol use.

Results: Of 32,254 participants, 3,633 reported functional thyroid disease (excluding neoplasms, congenital disease, nodules without functional changes, cysts, and unspecified type). Analyses were restricted to 2109 cases of functional thyroid disease with thyroid prescription medication use and validation through medical record review. In analyses starting at age 20 years or in 1952, thyroid disease hazard ratios across cumulative exposure quintiles were 1.00, 1.24, 1.27, 1.36, and 1.37 among women and 1.00, 1.12, 0.83, 1.01, and 1.05 among men (log-linear trend tests: $P = 0.03$ and $P = 0.85$, respectively); similar results were observed for yearly exposure. Associations were observed for hyperthyroidism and hypothyroidism among women. Some subanalyses also suggested an increased hazard of hypothyroidism among men.

Conclusions: Higher PFOA exposure was associated with incident functional thyroid disease in this large cohort with high exposure.

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Perfluorooctanoic acid (PFOA) is an environmentally persistent perfluorinated compound used in the manufacture of nonstick cookware and in coatings resistant to soil, water, stain, and grease.[1,2] Human exposure to PFOA comes primarily from food, drinking water, dust, and air.[3] PFOA is not metabolized in the human body and has a half-life of 2.3–3.4 years.[4–6] The 2003–2004 United States National Health and Nutrition Survey (NHANES) detected PFOA in the serum of >99% of the US population, with a median concentration of 4.0 μg/L.[7] Higher serum concentrations have been found in populations near facilities using PFOA.[2,8,9]

PFOA can disrupt thyroid hormone homeostasis in animals such as rats and primates.[2,10] In humans, some occupational studies have suggested an association between PFOA exposure and thyroid hormone levels, but findings have not been consistent.[11–13] Some nonoccupational epidemiologic studies have found no associations,[14–17] whereas others have found associations with thyroid disease[18,19] or thyroid hormone levels.[19–21] Most previous epidemiologic studies on PFOA and thyroid outcomes have been cross-sectional, have considered populations with limited exposure ranges (uniformly high or low), or have had relatively small study populations.

We assessed the association between estimated serum PFOA levels and thyroid disease in a large longitudinal cohort study with a wide PFOA exposure range. This study was conducted among a population exposed to PFOA released from a mid-Ohio River Valley chemical plant.[22] A class action lawsuit settlement funded an initial survey (the C8 Health Project, 2005–2006) of people exposed to PFOA-contaminated drinking water in specified water districts near the plant for at least 12 months during 1950–2004.[9,22] The settlement also funded a subsequent series of C8 Science Panel studies (including this study) conducted to determine whether there is a "probable link" between PFOA and human disease.

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METHODS

Cohort Recruitment and Survey Administration

This study included community and worker cohorts, which were combined for many analyses. The methods for cohort recruitment and survey administration have been previously described[23] and are briefly summarized here. Community cohort participants were recruited among 40,145 C8 Health Project participants who were at least 20 years old and consented to be contacted by the C8 Science Panel for further studies. Worker cohort participants were recruited from a previous occupational mortality study cohort of 6026 people who worked at the chemical plant during 1948–2002.[24] Some people (n = 2,090) were in both target cohorts. Study participants were asked to complete questionnaires during 2008–2010 and 2010–2011 covering demographics, health-related behaviors, and lifetime personal medical history. This study was approved by the Emory University Institutional Review Board.

Of 40,145 people in the community cohort target population, 32,712 (81%) completed a study questionnaire during 2008–2011; of these, 4152 plant workers were excluded from the community cohort. Among the remaining 28,560 community cohort participants, 28,541 (99%) had retrospective exposure estimates. Of 6026 people in the worker cohort target population, 4,391 (73%) completed a study questionnaire during 2008–2011, of whom 3,713 (85%) had retrospective exposure estimates.

Thyroid Disease Ascertainment and Classification

The 2008–2010 and 2010–2011 questionnaires included the question, "Have you ever been told by a doctor or other health professional that you had thyroid disease?" Participants answering "Yes" to this question were asked the thyroid disease type (goiter, Graves disease, Hashimoto's disease, hyperthyroidism, hypothyroidism, or "something else"—in which case they were asked to specify disease type) and whether they were currently taking prescription medication for thyroid disease. For each reported thyroid disease type, participants were asked their age at diagnosis. Participants reporting thyroid disease with thyroid prescription medication (79% of people reporting any thyroid disease) were asked for their consent to review of their medical records to confirm the diagnosis.

Functional thyroid disease was defined as a report of goiter, Graves disease, hyperthyroidism, Hashimoto's disease, hypothyroidism, thyroiditis not otherwise specified, or a thyroid function problem of unknown type. The definition of functional thyroid disease excluded neoplasms (benign and malignant); congenital disease; nodules, cysts, or a thyroidectomy without functional changes mentioned; and thyroid disease of unspecified type. People who reported thyroid disease not meeting the functional thyroid disease case definition (n = 1,045) were excluded from all analyses (including 700 with unspecified thyroid disease type [15% of thyroid disease reports] and 345 who reported thyroid disease of other types). Hyperthyroidism was defined as a report of hyperthyroidism or Graves disease. Hypothyroidism was defined as a report of hypothyroidism or Hashimoto's disease. In analyses specifically for hyperthyroidism and hypothyroidism, people reporting a prior diagnosis of disease of the other type were censored at the time of the other diagnosis, and those who reported both conditions with an uncertain sequence were excluded. Analyses were restricted to self-reported cases for which current thyroid medication was reported, and validation was obtained through review of medical records, excluding from the analysis cases without current thyroid medication or validation.

Retrospective Serum PFOA Concentration Estimates

Retrospective serum PFOA concentration estimates were from a multistage modeling procedure described in detail elsewhere[23,25,26] and briefly summarized here. Yearly air and drinking water PFOA concentrations were estimated using an environmental fate and transport model.[25] For the community cohort, air and water concentration estimates, together with information about residential history and drinking water consumption rates and sources, were used to estimate each person's yearly PFOA intake rate. Yearly intake rates were used in an absorption/distribution/metabolism/excretion model to generate yearly serum PFOA concentration estimates.[26] For plant workers, an occupational exposure model (using work history information along with modeled job- and department-specific serum concentration estimates) was used to generate yearly serum PFOA concentration estimates for years when they worked at the plant.[27] For years after workers stopped working at the plant, serum estimates were decayed at an annual rate of 18% until reaching the community exposure model estimates. Serum concentration estimates from the community model were used if they were higher than occupational model estimates. Among those with serum measurements from the C8 Health Project, the Spearman's rank correlation between measured and estimated PFOA serum concentrations in the year of the C8 Health Project, incorporating community and occupational exposure estimates, was 0.71.[23] The primary retrospective analyses used unadjusted serum estimates. For prospective analyses (examining new disease since the 2005–2006 C8 Health Project), estimates were generated using Bayesian calibration to adjust serum concentration estimates based on the 2005–2006 measurements, with measurements weighted more heavily in years closer to the measurement time.

Data Analysis

We assessed adult thyroid disease in relation to PFOA exposures in Cox proportional hazards models with time-varying exposure and covariates, using age as the time scale. Analyses excluded people born before 1920 because of uncertain reliability of retrospective disease reporting in this group (n = 173). Retrospective analyses started at the later of age

20 years (to consider only adult thyroid disease) or the age in 1952 (the year after PFOA production started at the plant). Prospective analyses started at the age at time of C8 Health Project participation (in 2005–2006). Both types of analyses excluded those with a thyroid disease diagnosis before the analysis start age. Analyses ended at the earliest of the age at thyroid disease diagnosis, death, or the last study questionnaire. All analyses were done using SAS version 9.2 (SAS Institute, Cary, NC).

Because the mechanisms through which PFOA might affect thyroid function are uncertain, we considered two different time-varying metrics for the serum PFOA concentration estimates. Analyses assessing short-term effects used time-varying yearly serum concentration estimates (the serum concentration estimate for the age at diagnosis or the corresponding age for noncases). Analyses assessing long-term effects used time-varying cumulative serum concentration estimates, defined as the sum of each person's yearly serum concentration estimates from birth through a given year. We also conducted prospective analyses using measured PFOA serum concentrations in 2005–2006 (not time-varying). The primary models considered patterns of hazard ratios (HRs) across quintiles of each exposure metric, with quintiles defined using the exposure estimates for self-reported cases of functional thyroid disease at the time of diagnosis for all analyses. In tests for trend, we used the natural log-transformed PFOA concentration estimates (which gave better model fit than untransformed estimates, by Akaike's information criterion). To examine the dose–response curve shape, we also considered retrospective analyses by PFOA exposure deciles.

Survival analyses adjusted for birth year, sex, race (white/nonwhite), years of schooling (not time varying; <12 years, high school diploma or equivalent, some college, or bachelor's degree or higher), smoking status (time varying; nonsmoker, current smoker, or former smoker), and regular alcohol use (time varying; no use, current use, or former use). We did not control for body mass index (BMI) due to lack of time-varying BMI information and concern that BMI measured only toward the end of the analytic period (sometimes after a thyroid disease diagnosis) could be affected by thyroid disease outcomes. Birth year and sex violated the proportional hazards assumption. All models were stratified by single-year birth year. We considered sex-specific models and models with a term for the interaction between sex and age.

The primary analyses considered the combined cohorts (88% community, 12% workers). To assess the potential for bias due to inclusion of workers, who might have had additional chemical exposures and been healthier overall, we also considered analyses restricted to the community cohort. To examine the extent to which results may have been affected by low exposures occurring before residence in the study area, and possible differential migration into the area by disease status, additional sensitivity analyses started at the first age at which each person was known to have qualified for one of the cohorts (by living in the study area for at least 1 year or working at the plant, referred to as "qualifying year"). To assess possible effect modification by calendar time, we considered models that ended the cohort follow-up (and hence the analysis) in varying calendar years, in 3-year intervals back to 1984 (before peak exposure).

RESULTS

Cohort Characteristics

Demographic characteristics of the cohorts are presented in Table 1. In the combined cohort, study participants were predominantly white (97%); 54% were women. The median follow-up duration was 32.6 years starting at the age in 1952 or at age 20 years, and 4.4 years starting at the time of the C8 Health Project. The median PFOA serum concentration measured in 2005–2006 was 26.1 ng/ml. Median estimated serum PFOA concentrations were highest in the late 1990s and early 2000s.[23]

Thyroid Disease Reports

In the combined cohorts, 4678 people self-reported any thyroid disease diagnosis; 3633 reported disease classified as functional thyroid disease, with 780 classified as hyperthyroidism and 2,395 classified as hypothyroidism (Table 2). The number of thyroid disease cases was substantially higher among women. The median age at diagnosis for functional thyroid disease was 42 years (40 years among women, 50 years among men). Among people reporting disease classified as functional thyroid disease, 83% reported taking current prescription medication for thyroid disease. Medical records were reviewed for 77% of these cases, and 91% of reviewed cases were confirmed for functional thyroid disease.

Survival Analysis Results

The primary retrospective survival analyses showed increasing hazards of validated functional thyroid disease with increasing estimated PFOA exposure quintiles, overall and among women (Figure 1; tabular results in eTable 1, http://links.lww.com/EDE/A748). Using the cumulative exposure metric, the HRs for functional thyroid disease for quintiles 2–5 versus quintile 1 were 1.21, 1.17, 1.27, and 1.28 for the sexes combined (log-linear trend test: HR per log μg/ml·yr = 1.03, $P = 0.09$). The trend was more pronounced among women (HRs for quintiles 2–5 vs. quintile 1 = 1.24, 1.27, 1.36, and 1.37; HR per log μg/ml·yr = 1.04, $P = 0.03$) and was absent among men (HRs for quintiles 2–5 vs. quintile 1 = 1.12, 0.83, 1.01, and 1.05; HR per log μg/ml·yr = 1.01, $P = 0.85$). Using the yearly exposure metric, the HRs for functional thyroid disease for quintiles 2–5 versus quintile 1 were 1.23, 1.24, 1.10, and 1.28 for the sexes combined (HR per log ng/ml = 1.03, $P = 0.04$). The trend was again more pronounced among women (HRs for quintiles 2–5 vs. quintile 1 = 1.26, 1.28, 1.11, and 1.38; HR per log ng/ml = 1.04, $P = 0.008$) and was absent among men (HRs for quintiles 2–5 vs. quintile 1 = 1.13, 1.11, 1.06, and 1.04; HR per log ng/ml = 1.00,

TABLE 1. Characteristics of the Cohort (n = 32,254)

Characteristic	Community Cohort Only (n = 28,541)	Worker Cohort (n = 3,713)	Combined Cohorts (n = 32,254)
Year of birth			
25th percentile	1947	1941	1946
Median	1958	1951	1957
75th percentile	1970	1963	1969
Sex; no. (%)			
Women	16,602 (58)	758 (20)	17,360 (54)
Race; no. (%)			
White, non-Hispanic	27,901 (98)	3,284 (88)	31,185 (97)
Other	640 (2)	134 (4)	774 (2)
Missing	0	295 (8)	295 (1)
Education; no. (%)			
<High school	3,026 (11)	37 (1)	3,063 (9)
High school	11,706 (41)	1,265 (34)	12,971 (40)
Some college	9,441 (33)	1,081 (29)	10,522 (33)
College diploma or higher	4,366 (15)	1,328 (36)	5,694 (18)
Missing	2 (0)	2 (0)	4 (0)
Smoking; no. (%)			
Never smoked	13,527 (47)	1,989 (54)	15,516 (48)
Smoked and quit	8,899 (31)	1,297 (35)	10,196 (32)
Smoked, did not quit	6,115 (21)	427 (12)	6,542 (20)
Regular alcohol consumption; no. (%)			
Never	17,011 (60)	1,683 (45)	18,694 (58)
Yes and quit	4,105 (14)	535 (14)	4,640 (14)
Yes, did not quit	7,360 (26)	1,486 (40)	8,846 (27)
Missing	65 (0)	9 (0)	74 (0)
Source cohort; no. (%)			
Community cohort only	28,541 (100)	0	28,541 (88)
Both community and worker cohorts	0	1,890 (51)	1,890 (6)
Worker cohort only	0	1,823 (49)	1,823 (6)
Serum PFOA concentration measurement from the C8 Health Project (2005–2006) (ng/ml)			
Mean	70.9	324.6	86.6
Standard deviation	151.2	920.6	278.9
25th percentile	12.3	55.9	12.8
Median	24.2	112.7	26.1
75th percentile	58.9	256.2	68.1
Number with measurements	28,422	1,881	30,303
Length of follow-up[a] (years)			
Mean	31.8	38.1	32.6
Standard deviation	15.0	12.6	14.9
Median	32.0	39.0	32.8

[a]Starting at the later of the age in 1952 or age 20 years.

$P = 0.97$). The number of functional thyroid disease cases was smaller among men, and there was not strong statistical evidence of interaction between exposure and sex (P values for interaction terms between sex and log PFOA concentration: 0.99 for cumulative metric and 0.27 for yearly metric).

A trend of increasing hazards with increasing exposure was suggested for both hyperthyroidism and hypothyroidism in relation to cumulative exposure (although log-linear trend P values were >0.05) and for hyperthyroidism in relation to yearly exposure (log-linear trend P values <0.05 for hyperthyroidism, overall and among women). Trends for the disease types were strongest among women, but again there was no strong statistical evidence of interaction between exposure and sex (P values for interaction terms between sex and log

TABLE 2. Thyroid Outcome Frequencies, Combined Community, and Worker Cohort

Outcome and Sex	No. Self-reporting Outcome	No. Reporting Current Medication (% of Self-reported Cases)	No. with Medical Record Reviewed (% of Reported Cases with Medication)[a]	No. Validated (% of Reviewed)	No. Validated Cases in Retrospective Analysis[b]	No. Validated Cases in Prospective Analysis[c]
			Functional thyroid disease			
Total	3,633	3,027 (83)	2,323 (77)	2,109 (91)	2,008	454
Men	654	561 (86)	426 (76)	384 (90)	376	110
Women	2,979	2,466 (83)	1,897 (77)	1,725 (91)	1632	344
			Hyperthyroidism[d]			
Total	780	597 (77)	456 (76)	400 (88)	384	72
Men	174	128 (74)	95 (74)	80 (84)	80	15
Women	606	469 (77)	361 (77)	320 (89)	304	57
			Hypothyroidism[e]			
Total	2,395	2,146 (90)	1,655 (77)	1,442 (87)	1,368	302
Men	415	387 (93)	298 (77)	252 (85)	245	71
Women	1,980	1,759 (89)	1,357 (77)	1,190 (88)	1,123	231

[a]Although medical records validation for thyroid disease was generally limited to self-reported cases of thyroid disease with current medication, two cases of hyperthyroidism were reviewed (one confirmed) among people who did not report current medication.

[b]People were excluded from the analyses if they reported thyroid disease but were missing the age at diagnosis or had an invalid age at diagnosis (38 for functional thyroid disease, 13 for hyperthyroidism, and 39 for hypothyroidism), or if they had an age at diagnosis before age 20 (208 for functional thyroid disease, 43 for hyperthyroidism and 126 for hypothyroidism). Additional cases were excluded due to exclusion of all time before 1952 (resulted in exclusion of 21 cases of functional thyroid disease, 5 cases of hyperthyroidism, and 10 cases of hypothyroidism), exclusion of all people born before 1920 (resulted in exclusion of 14 cases of functional thyroid disease, three cases of hyperthyroidism, and seven cases of hypothyroidism), and exclusion of people with missing values for variables in the model (missing values for education resulted in exclusion of one case of functional thyroid disease, missing values for alcohol resulted in exclusion of one case of functional thyroid disease and one case of hypothyroidism).

[c]Reasons for exclusion from the prospective analysis were the same as those for the retrospective analysis with the additional exclusion of those who did not participate in the C8 Health Project (and thus did not have estimates with Bayesian calibration) and those who developed thyroid disease before the time of the C8 Health Project.

[d]Excluding those with prior diagnosis of hypothyroidism.

[e]Excluding those with prior diagnosis of hyperthyroidism.

PFOA concentration were between 0.23 and 0.88 for the various outcomes and metrics).

Supplementary analyses restricted to the community cohort yielded similar results (eTable 2, http://links.lww.com/EDE/A748), and there was no statistical evidence of a difference in associations between cohorts (for the interaction term between cohort and log PFOA concentration in analyses for validated functional thyroid disease, sexes combined: $P = 0.31$ for cumulative metric, 0.48 for yearly metric). Other supplemental analyses starting at the age in each person's "qualifying year" had fewer cases and showed generally weaker trends than the primary analysis. Nevertheless, this analysis did show an increasing hazard for hyperthyroidism with increasing yearly PFOA exposure, especially among women (combined cohort results in eTable 3, http://links.lww.com/EDE/A748, community cohort results in eTable 4, http://links.lww.com/EDE/A748). Finally, supplemental analyses further examining the dose–response curve shape through analyses by PFOA exposure deciles (eFigure 1, http://links.lww.com/EDE/A748) showed an initial increase in hazard at low exposure levels with a slower increase in hazard at higher exposure levels, similar to quintile analyses.

The prospective analyses using estimates with Bayesian calibration showed no clear associations between PFOA and functional thyroid disease in analyses with both sexes combined (Figure 2, tabular results in eTable 5, http://links.lww.com/EDE/A748), but the number of cases was much smaller than in the retrospective analysis and confidence intervals were wide. There was a suggestion of an increasing hazard of functional thyroid disease with increasing cumulative exposure among men (HRs for quintiles 2–5 vs. quintile 1 = 1.35, 1.37, 1.44, 1.85; HR per log μg/ml·yr = 1.14, $P = 0.09$). Among men, the hazard of hypothyroidism increased with increasing PFOA exposure in analyses considering the cumulative and yearly exposure metrics, as well as analyses using measured PFOA serum concentrations in 2005–2006, being most evident in the cumulative exposure metric analyses (HRs for quintiles 2–5 vs. quintile 1 = 1.12, 1.32, 1.45, 2.02, HR per log μg/ml·yr = 1.24, $P = 0.021$). There was statistical evidence of interaction between sex and exposure in the prospective analysis for hypothyroidism with the cumulative exposure metric (P value for interaction term = 0.009), with higher HRs among men. Prospective analyses restricted to the community cohort yielded similar results (see eTable 6, http://links.lww.com/EDE/A748), and there was no statistical evidence of a difference in associations between cohorts (P value for interaction term between cohort and log PFOA concentration in analyses for validated functional thyroid disease, sexes combined: 0.32 for cumulative metric and 0.29 for yearly metric).

The results of retrospective analysis assessing possible effect modification by calendar time are shown in Figure 3. Within the time frame considered, for functional thyroid

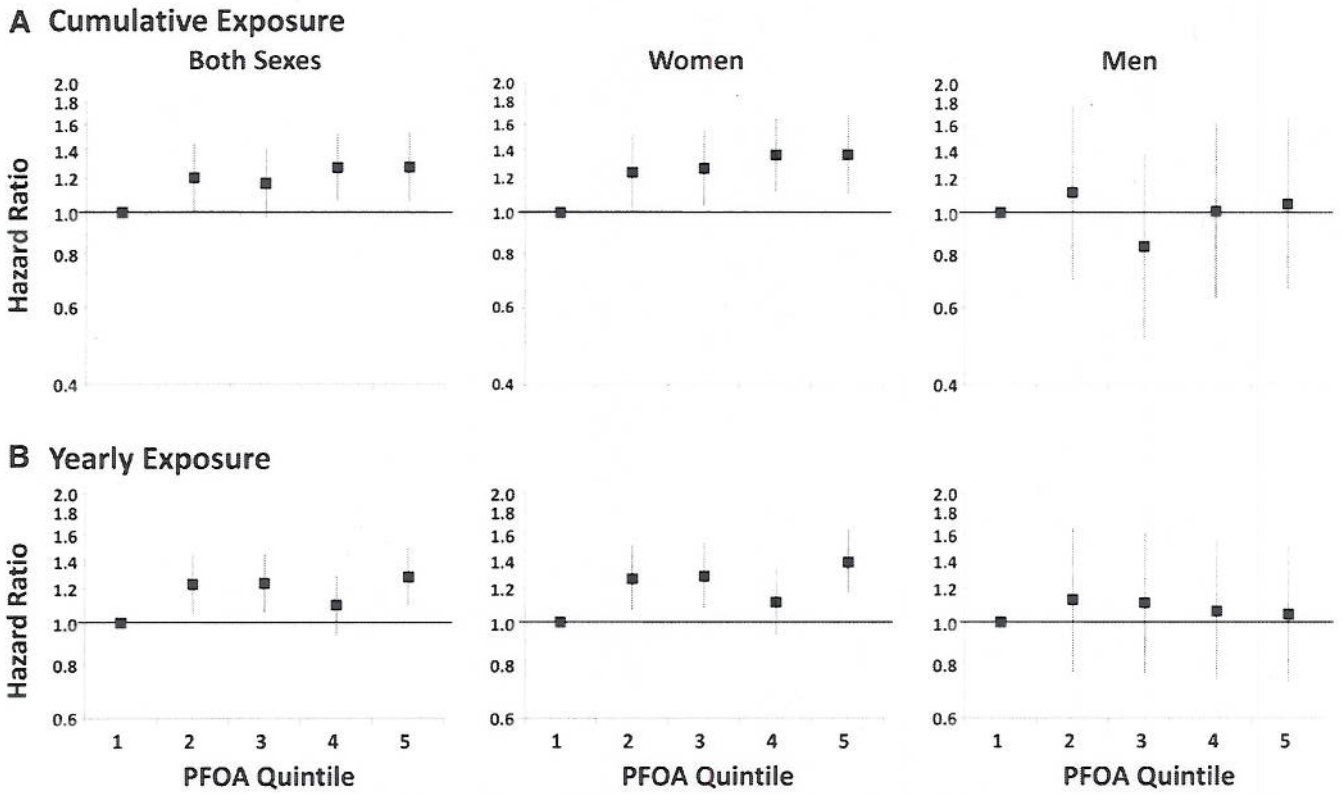

FIGURE 1. Retrospective survival analysis results for validated thyroid disease in relation to PFOA exposure estimates in combined cohorts. Black squares indicate hazard ratios; vertical bars indicate 95% CIs. A, Quintiles for cumulative exposure had the following cut points (in μg/ml·yr): 0.0001 to <0.1147, 0.1147 to <0.2022, 0.2022 to <0.4973, 0.4973 to 2.676, 2.676 to 97.396. B, Quintiles for yearly exposure had the following cut points (in ng/ml): 0.1061 to <4.7424, 4.7424 to <8.4889, 8.4889 to <21.583, 21.583 to <100.14, 100.14 to 3303.3.

disease the highest HRs for the trend tests for the log cumulative and log yearly serum PFOA concentration estimates were observed for analyses ending in 1990–1993, with progressively lower HRs observed for analyses ending in later years. When examined by quintiles for the years 1990 and 1993 (1993 shown), there was evidence of a monotonic increase in the hazard of functional thyroid disease across quintiles, especially for the yearly exposure metric.

DISCUSSION

We found evidence of an association between PFOA exposure and functional thyroid disease, especially for hyperthyroidism among women (in retrospective analyses) and for hypothyroidism among men (in prospective analyses). Results presented through 2011 may be conservative estimates of the strength of the associations with functional thyroid disease because observed associations were stronger if analyses were ended in years closer to the time of peak exposure.

Several mechanisms may underlie associations between thyroid disease and environmental exposures.[18,28,29] Some mechanisms, such as actions on thyroid hormone receptors or on deiodinases, might be more consistent with an association with yearly estimates, whereas other mechanisms, involving long-term effects on the thyroid gland, might be more consistent with an association with the cumulative estimates. Information about specific mechanisms through which PFOA may affect thyroid homeostasis is sparse; suggested mechanisms include binding to transthyretin or other binding proteins,[2,30–32] reduction in hypothalamic-pituitary axis responsiveness (seen for a related chemical, perfluorodecanoic acid),[2] enhancement of thyroid hormone degradation in the liver,[18] nuclear receptor binding,[18] and changes in thyroid hormone–binding protein production.[20] PFOA has been found in thyroid tissue but does not appear to be actively concentrated there.[33]

This study has several strengths. It is the largest study to date of the association between PFOA exposure and thyroid disease and was conducted in a population with a wide range of PFOA exposure levels. Novel aspects of the study include the longitudinal study design with yearly estimates of serum PFOA concentrations throughout life, information about specific thyroid disease diagnoses (including age at diagnosis), medical record validation of self-reported cases, and consideration of both cumulative and yearly exposure metrics.

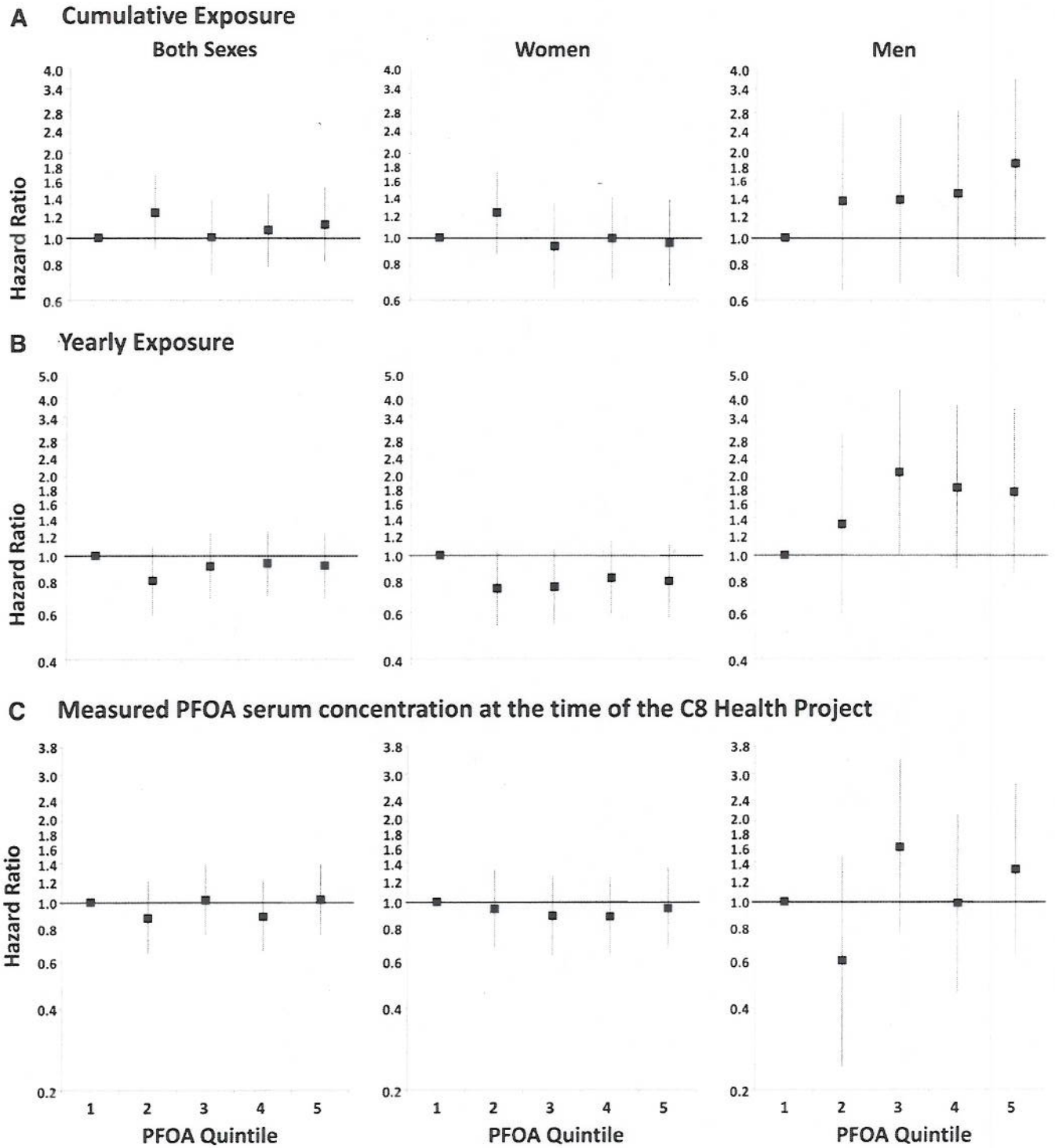

FIGURE 2. Prospective survival analysis results for validated thyroid disease in relation to PFOA exposure estimates in combined cohorts. Black squares indicate hazard ratios; vertical bars indicate 95% CIs. A, Quintiles for cumulative exposure had the following cut points (in μg/ml·yr): 0.0954 to <0.2170, 0.2170 to <0.3526, 0.3526 to <0.7066, 0.7066 to <2.3292, 2.3292 to 27.516. B, Quintiles for yearly exposure had the following cut points (in ng/ml): 2.662 to <5.366, 5.366 to <9.222, 9.222 to <17.075, 17.075 to <40.859, 40.859 to 991.25. C, Quintiles for measured values at the time of the C8 Health project had the following cut points (in ng/ml): 0.8 to <9.6, 9.6 to <17.4, 17.4 to <32.2, 32.2 to <84.7, 84.7 to 3167.9.

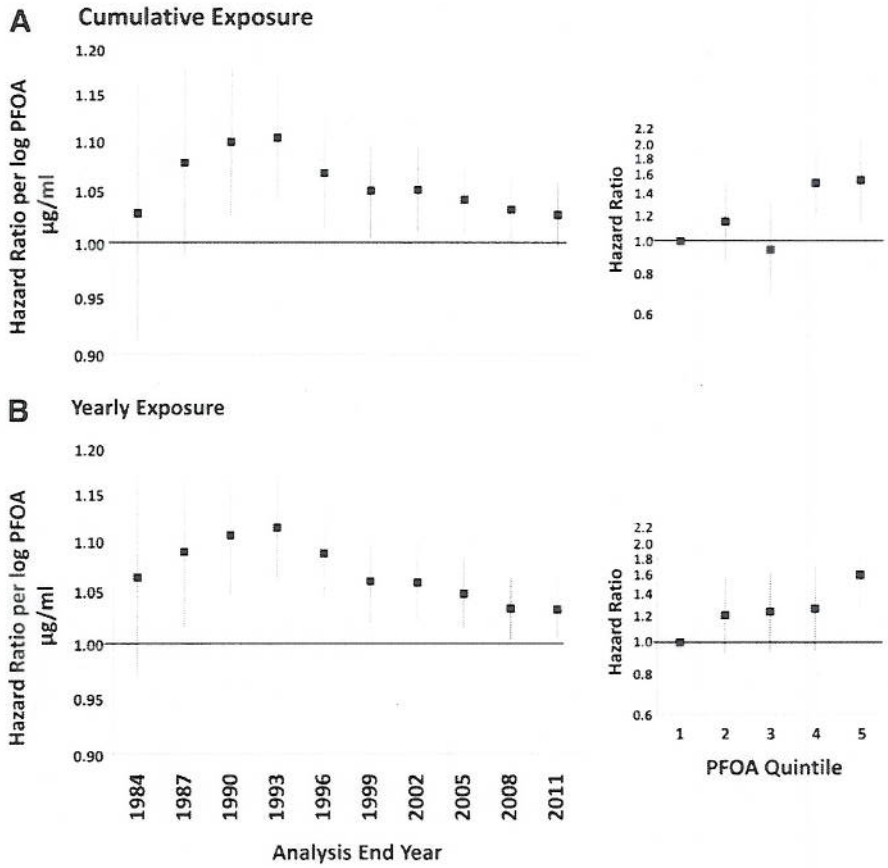

FIGURE 3. Results of assessment of possible effect modification by calendar time for validated thyroid disease in retrospective analyses, sexes combined. Black squares indicate hazard ratios; vertical bars indicate 95% CIs. A, Cumulative exposure; B, yearly exposure. Hazard ratios are for log-linear trend tests (per log unit PFOA concentration in µg/ml·yr for cumulative exposure estimates and ng/ml for yearly exposure estimates) or for quintiles 2–5 relative to quintile 1. For quintile analysis, the end year is 1993.

This study also has limitations. The population in the study area changed over time, and there was no way to identify and include all residents over the exposure period. If both PFOA exposure and thyroid disease affected (positively or negatively) the likelihood of being eligible for and participating in this study, the result could be bias in observed associations between PFOA and thyroid disease.[34] Such bias could potentially increase or decrease the magnitude of observed associations, depending on the nature of the associations between thyroid disease or PFOA exposure and eligibility/participation. To be in the community cohort, a person had to have participated in the C8 Health Project, which included only people who had lived in the study area for at least 1 year and were alive and available for study in 2005–2006. People no longer living in the study area at the time of the C8 Health Project may have been less likely to have been aware of, and participate in, the study. Workers did not have to be alive in 2006–2008, but workers who had died would be less likely to be included in the study due to difficulties in obtaining information from proxies. Therefore, if both exposure and disease affected survival, migration into or out of the study area, or willingness to participate in the study, selection bias could have affected the results. Although extreme hyperthyroidism or hypothyroidism can be fatal, most thyroid disease cases are not fatal, and the relationship between milder thyroid disease and overall mortality is not clear.[35] We assessed the potential impact of differential migration into the area on the results through sensitivity analyses restricted to time after a person was first known to have lived in the area or worked at the plant. Those analyses had lower power than our primary analyses but still showed associations between PFOA exposure and thyroid disease.

Another potential source of bias is possible changes in population susceptibility over time. Applebaum et al[36] showed that, when susceptibility to the effect of exposure on disease varies in a population, the initiation of observation after an ongoing exposure has been occurring for some time can lead to modest downward bias in effect measures due to decreasing susceptibility in the remaining population over time. The degree of bias increases with increasing time between first exposure and the start of observation. This problem may have led to downward bias in our prospective analysis results because those analyses started late in the exposure history and were conditioned on absence of disease to that point. Even if observation begins when exposure starts, with a long follow-up duration, variation in susceptibility to the effects of exposure on disease can result in a progressively less susceptible population remaining over time. This problem, inherent in the use of hazard models,[34,37] will cause decreasing HRs with increasing follow-up time.[37] We saw some evidence of

decreasing population susceptibility to PFOA effects over time in our retrospective analyses stopping at varying points in calendar time. Selection bias (greater participation by highly exposed earlier cases) could be an alternate explanation of those findings.

Other limitations relate to potential error in the exposure estimates and disease classification. Error in exposure estimates is likely independent of disease status and would most likely (but not certainly) bias exposure-outcome associations toward the null. Review of medical records increased the specificity of disease classification. However, thyroid disease cases could have been missed due to lack of recall, disease awareness, or prescription medication use, which could be related to access to care and socioeconomic status (SES). We also excluded people who reported thyroid disease (n = 700) with no type specified. Underdetection and exclusion of thyroid disease cases, if associated with exposure, could lead to bias. The age- and sex-adjusted prevalence of all self-reported thyroid disease among our study participants in 2005 (8–10%, depending on assumptions for missing age at diagnosis) was comparable to or slightly higher than the prevalence of self-reported thyroid disease in NHANES 1999–2002 (7.3%),[38] providing some reassurance on the completeness of thyroid disease reporting. We cannot evaluate the impact of access to care or SES on case ascertainment, but there was little evidence of a consistent association between SES and PFOA serum concentration estimates in these data.[23] Exclusion of people who reported no thyroid disease type was unlikely to bias our results because differences in exposure (measured PFOA serum concentrations in 2005–2006 or cumulative PFOA serum levels at age 20 years) between people who reported thyroid disease with and without a type (adjusting for other variables in our models) were relatively small.

Some previous studies among workers[11] and populations outside occupational settings[14–17] have found no association between PFOA and thyroid hormone levels or disease, whereas other studies have found associations.[12,13,18–21] Among studies that have found associations, results regarding specific types of thyroid function changes have not been consistent between studies. A medical surveillance study of workers in two fluorochemical production facilities found a positive association between PFOA and triiodothyronine (T3) levels in cross-sectional models but no association with thyroid-stimulating hormone (TSH) or thyroxin (T4).[12] A separate study, restricted to male employees not taking cholesterol-lowering medication, found higher serum PFOA concentrations to be associated with lower levels of free T4 and higher levels of T3. However, few thyroid hormone measurements were outside reference ranges, and no associations were found between PFOA and total T4 (TT4) or TSH.[13] A cross-sectional study of 3,966 NHANES participants 20 years of age and older found a positive association between serum PFOA concentrations and self-reported thyroid disease among women and men (with little statistical evidence of interaction between serum PFOA concentrations and sex).[18] Specific thyroid disease types were not examined in that study.

Three previous studies have been conducted in the same Ohio-Valley population as the current study. Two examined cross-sectional associations among adults without a reported history of thyroid disease. One of them found a positive association between serum PFOA levels and T4 in women and in men over 50 years in age, but no association with TSH.[20] The other found a positive association between PFOA and TSH in both sexes, positive associations between PFOA and both free thyroxine index and TT4 among women, and an inverse association between PFOA and subclinical hyperthyroidism.[21] In that second study, PFOA concentration changes were not associated with thyroid hormone level changes over a 5-year period. The third study found a positive association between measured PFOA concentrations and self-reported thyroid disease (and hypothyroidism specifically) among children 1–17 years of age.[19]

Our study adds to a growing body of literature, indicating an association between PFOA and thyroid homeostasis disruption. Further studies are needed to clarify the mechanisms through which PFOA may alter thyroid homeostasis.

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