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Time Trends in Per- and Polyfluoroalkyl Substances (PFASs) in California Women: Declining Serum Levels, 2011–2015

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ABSTRACT: After several decades of widespread use, some per- and polyfluoroalkyl substances (PFASs) were phased-out of use due to concerns raised by their persistent, bioaccumulative, and toxic properties. Our objective was to evaluate temporal trends in serum PFAS levels among 1257 middle-aged and older California women (ages 40–94) during a four year period, beginning approximately 5–10 years after these phase-outs began. An online SPE-HPLC-MS/MS was used to measure 10 long-chain PFASs in serum from blood collected cross-sectionally during 2011–2015 from a subset of participants in the California Teachers Study. Results from multivariable linear regression analyses indicated that serum concentrations of nearly all PFASs declined on average 10% to 20% per year. Serum levels of perfluorohexanesulfonic acid (PFHxS) did not significantly decline. With the exception of PFHxS, the downward trend in serum concentrations was evident for all PFASs across all ages, although declines were comparatively steeper among the oldest women. These findings suggest that the phase-out of some common PFASs has resulted in reduced human exposures to them. The lack of a decline for PFHxS suggests that these exposures may be ongoing and underscores the importance of continued biomonitoring and research efforts to elucidate current pathways of exposure.

INTRODUCTION

Per- and polyfluoroalkyl substances (PFASs) are a large group of synthetic fluorinated chemicals widely used in industrial processes and consumer products since the 1950s.^{1,2} Owing to their persistent and bioaccumulative properties, some of these compounds emerged during the 1990s as among the most pervasive global environmental contaminants²⁻⁵ and biomonitoring data indicated evidence of human exposures.⁶⁻⁸ Coupled with accumulating evidence of myriad toxic and potential adverse health effects,^{2,9-16} regulatory restrictions and voluntary phase-outs of many of these compounds were enacted shortly after the beginning of the 21st century, internationally as well as within the United States.^{2,13,17}

Representing a broad class of chemicals, the PFASs encompass a large number of compounds with a diversity of chemical properties that determine not only their toxicity but also their persistence.^{1,18,19} Hence, manufacturing and use restrictions have been targeted at what are considered the most worrisome chemicals within the class of PFASs. Attention has focused predominantly on the highly persistent fully fluorinated perfluoroalkyl acids (PFAAs) rather than the partially fluorinated and less persistent polyfluoroalkyl substances. Within the class of PFAAs, the longer chain compounds are more toxic and more resistant to chemical and biological degradation.^{1,17} Additionally, the perfluoroalkyl sulfonic acids (PFSAs), of which perfluorooctanesulfonic acid (PFOS) is the most well-studied, are comparatively more persistent than the perfluoroalkyl carboxylic acids (PFCAs),¹⁷ of which perfluorooctanoic acid (PFOA) is the most notable. For these reasons, sulfonic acids with 6 or more carbons ($\geq C6$) and carboxylic acids with 7 or more carbons ($\geq C7$), which are defined as long-chain PFAAs,¹ have been the target of most of the regulatory and voluntary measures implemented to date. Prior to 2002 when 3M, the primary global manufacturer of PFOS, voluntarily ceased its production,²⁰ PFOS was the predominant PFAA in use. Further efforts to reduce global PFOS emissions were reinforced in 2006 by European Union (EU) restrictions on its use and marketing²¹ and by the addition of PFOS to the Stockholm Convention in 2009.²² Following these measures, global production of PFOS reportedly dropped, while PFOA production increased dramatically.¹³ In 2006, under the United States Environmental Protection Agency's (US EPA) 2006 PFOA Stewardship Program, eight of the largest users and producers of PFOA committed to reduce global emissions and use of PFOA, its precursors, and other long chain PFAAs, by 95% by 2010 and completely eliminate them by 2015.²³ Some companies reported reaching the complete elimination goal by 2013.²⁴

Despite these phase-out efforts, exposures to PFAAs are likely to still occur for a number of reasons. Reported reductions in PFAAs are based on voluntary industry reports and have not necessarily been verified. The long half-lives and bioaccumulative nature of some of these compounds^{18,19,25} ensure that exposures will continue for a number of years after production and use have ceased. While restrictions in North America, Europe, Australia, and Japan have been enacted, PFAAs are still being produced in large quantities in other areas of the world.^{4,26} The well-documented dispersion of PFAAs contamination to all corners of the world, including the far reaches of the Arctic,^{2,13,17} underscores the long-range transport of these compounds beyond the borders of where they are manufactured and used. Furthermore, in regions where longer chain PFAAs have been phased-out, shorter chain PFAAs, which remain comparatively understudied, are being introduced as replacements.^{17,27} Finally, exposures to PFAAs may occur indirectly through exposures to biotransformation byproducts of precursor compounds.^{1,4,5,17}

As concerns over potential human health effects associated with these compounds are mounting, biomonitoring data offer a critical tool for evaluating the effectiveness of these

regulatory and voluntary restrictions in mitigating human exposures to PFASs. Published summaries of biomonitoring data suggest mixed success. While body burden levels of PFOS and PFOA appear to have declined since the early 2000s, in some cases rather dramatically,^{2,28–45} evidence indicates that body burden measures of certain PFASs, particularly some of the other long-chain PFAAs, have not declined and may be increasing.^{7,28,31,35–39,42,45}

The objective of the current analyses is to describe serum levels of PFASs in a large sample of middle-aged and older California women in blood collected cross-sectionally from 2011 through 2015 and to evaluate temporal trends in serum levels across the approximate 4 year period of blood collection.

■ MATERIALS AND METHODS

Study Population. The study population consisted of 1257 participants selected as a subset from the California Teachers Study (CTS), a prospective cohort study that recruited 133 479 female public school professionals in 1995–1996 primarily to study breast cancer. A full description of the cohort is available elsewhere.⁴⁶ All women included in the current analysis lived in California continuously since joining the CTS and were serving as controls in an ongoing breast cancer case-control study nested within the CTS or were recruited separately in a convenience sample of cancer-free CTS participants which targeted nonwhites to enhance racial/ethnic diversity. Controls in the case-control study were drawn from a probability sample of at-risk cohort members frequency-matched to breast cancer cases by age, race/ethnicity, and broad geographic region (corresponding to the three field collection sites). The convenience sample was drawn from a probability sample of cancer-free CTS members under 80 years of age who self-reported as Non-Hispanic White, Black, Hispanic, or Asian/Pacific Islander and were geographically distributed so as to provide a balanced representation of urban and rural residences. All participants included in the current analysis completed an interviewer-administered questionnaire at the time of blood draw. Participants ranged in age from 40 to 94 years, were primarily postmenopausal (91%), and non-Hispanic white (75%). The use of human subjects was reviewed and approved by the California Health and Human Services Agency, Committee for the Protection of Human Subjects and the Institutional Review Boards of participating study institutions.

Serum Collection. One blood specimen from each study participant was collected between May 9, 2011 and August 24, 2015 by licensed phlebotomists, usually in the participants' homes. Blood was collected into a 10 mL BD tube (catalog#367985, Becton Dickinson, Franklin Lakes, NJ) with clot activator, double gel for transport, and silicone coated interior using standard phlebotomy techniques. Prior to field processing, specimens were kept on cool packs for at least 30 min. Within hours of collection, phlebotomists spun down the clotted blood samples in the field using portable centrifuges to separate the serum portion. Processed samples were then frozen and stored at –20 °C for 4–6 weeks until transported either via local courier (on cool-packs) or overnight (on dry ice via FedEx) to the laboratory for chemical analysis. Samples remained frozen during this transportation process. Upon receipt at the laboratory, specimens were stored at –20 °C until analysis.

Serum PFASs Measurements. Measurements of PFASs were conducted, using an online SPE-HPLC- MS/MS method as described in the Supporting Information and detailed

previously.⁴² Briefly, 100 µL of serum was diluted in formic acid and spiked with isotopically labeled internal standards before injection into the online SPE-HPLC-MS/MS system (Symbiosis Pharma, IChrom Solutions, Plainsboro, NJ, and Sciex4000 QTrap mass spectrometer, Sciex, Redwood City, CA) for cleanup and analysis. Native and isotopically labeled PFAS standards were purchased from Wellington Laboratories (Shawnee Mission, KS). Within each batch analysis of 20 actual samples, two in-house spiked calf serum samples and NIST 1958 Standard Reference Material were run in duplicate for quality control. While 12 PFASs were measured, perfluorobutanesulfonic acid (PFBS) and perfluorododecanoic acid (PFDoDA) were excluded from this study due to low detection frequencies (DFs) which were 18.9% and 9.6%, respectively.

Covariate Selection. While the data collected from CTS participants were not specifically designed to evaluate temporal trends in PFASs, considerable information on potential covariates was available from a number of CTS surveys. Data on race/ethnicity, birthplace, body mass index (BMI), physical activity (hours/week), alcohol consumption (grams/day), smoking status, duration of breastfeeding, and number of full-term pregnancies were derived from responses to the 1995–1996 baseline questionnaire administered to the full CTS cohort.⁴⁶ Quartiles for dietary consumption (grams/day) of meat, eggs, fish, and protein were derived from information on dietary factors obtained from responses to a modified version of the Block questionnaire included in this questionnaire.^{47,48} Additionally, indicators for dietary patterns (plant-based, high protein/fat, high carbohydrate, ethnic, and salad/wine) as previously developed⁴⁹ were considered as potential covariates. A variable for weight change was calculated based on information reported on the fifth mailed questionnaire (administered in 2012–2013) and the 1995–1996 baseline questionnaire. Responses to a short questionnaire administered by the phlebotomist at the time of blood collection were used to generate variables for age (years), menopausal status (postmenopausal/ premenopausal/perimenopausal), age at menopause (years), fingernail biting (yes/no), frequency of hand washing before eating, percent of home that is carpeted, and year home was built. Season of blood collection (winter = December–February; spring = March–May; summer = June–August; fall = September–November) was based on the date that the blood sample was collected, as recorded by the phlebotomist. This set of potential covariates was based on a priori knowledge based on a review of the relevant literature.

In addition to these survey-based factors, a number of neighborhood factors were also considered as potential covariates. Neighborhood socioeconomic (SES) characteristics were derived by linking the location of participants' residences to U.S. Census data. ArcGIS, version 9.2 (ESRI Redlands, CA, U.S.A.) was used to geocode the participants' home addresses at the time of blood draw to a U.S. Census 2010 block group. Based on these data, we assigned a composite measure of neighborhood SES to each participant using a previously developed method that incorporates census-based measures of income, occupation, and education.⁵⁰ This variable was then categorized into quintiles. Similarly, neighborhood urbanization was characterized based on 2010 U.S. Census data for the block group of residence at the time of blood collection, adapting a previously developed method to characterize neighborhood urbanization into four categories (rural/town, city, suburban, and metro).^{51,52}

A prior analysis of serum PFAS levels in a slightly different subset of the CTS suggested an association between serum PFAS levels and living in a zip code served by a public water system with PFASs detected in the water supply.⁵³ As a follow-up to those earlier analyses, we

considered indicators for PFAS detection in drinking water (based on the data and methods previously described⁵³) as potential covariates in the current analysis. Because levels of detection (LOD) varied for each compound by laboratory batch, the LOD was also considered as a potential confounding factor.

Statistical Analysis. In order to be consistent with published data from the National Health Nutrition Examination Survey (NHANES) and other biomonitoring studies, serum samples with PFAS concentrations below the LOD were imputed as $\text{LOD}/\sqrt{2}$.^{54,55} To compare PFAS levels to national biomonitoring data, laboratory data from NHANES for the periods 2011–2012 and 2013–2014 were downloaded,^{56,57} and geometric means and 95% confidence intervals (95% CIs) were calculated for the subset of NHANES participants who were non-Hispanic white females and aged 40 years or older. These comparisons were conducted only for the 6 PFASs that were detected in >65% in both our study population and the analogous subset of NHANES. To assess correlations between the PFAS compounds, which exhibited skewed distributions, Spearman Rank Correlation Coefficients were computed.

Multivariable linear regression models were used to assess temporal trends in serum PFAS concentrations. Blood sample collection dates were converted to a continuous “time-years” variable, a real number representing the number of years and fraction of years since January 1, 2011. PFAS serum concentrations were $\log_{10}$ -transformed to normalize the skewed distributions and then regressed on time-years, adjusting for potential confounders. Only factors that were identified as statistically significant ($p \leq 0.05$) in backwards stepwise linear regression modelling or that changed the regression coefficient of the time-years variable by 10% or more were retained in the final regression models. To evaluate the potential for nonlinear time trends, time-years was also entered into the backwards stepwise models as a quadratic term. For PFHpA, PFNA, and PFDA the quadratic term for time-years was significant ($p \leq 0.05$) and was retained in the regression models. We present results from both the crude and multivariable-adjusted regressions. Multivariable model building resulted in different models for each PFAS (see footnote of Table 3 for specific covariates included in each of the final models). The explanatory power of the final regression models was quite modest, with R-squared (R^2) values ranging from 0.11 (for PFOA) to 0.23 (for PFUnDA). To assess whether temporal patterns were consistent across age groups, we repeated the regression analyses, stratified by broad age categories (40–59 years, 60–69 years, and ≥ 70 years). Due to some small cellcounts, these age-stratified regressions were adjusted for race/ethnicity and age (continuous years) only.

To facilitate interpretation of our regression results, the time trend β coefficients for the linear and quadratic terms for time-years were used to create a summary average annual percent change (aAPC). The aAPC was calculated in three steps. First, for convenience only, the trend coefficients were recalculated assuming the concentrations were transformed by taking natural logs, rather than $\log_{10}$, producing transformed coefficients (β_1, β_2). Note that for all but three PFASs (PFHpA, PFNA, and PFDeA), the quadratic term for time-years was not significant, rendering $\beta_2 = 0$. Second, the transformed time trend coefficients were used to estimate an average relative growth rate $\text{aRGR} = \beta_1 + 5\beta_2$ by averaging the instantaneous relative growth rate, $\text{RGR}(t) = \beta_1 + 2\beta_2 t$, over the time interval $[0, 5]$. Finally, the aRGR was transformed into an aAPC using the standard formula $\text{aAPC} = 100(\exp(\text{aRGR}) - 1)$.

■ RESULTS

Table 1 summarizes the distribution of age and race/ethnicity by year of sample collection for the 1257 women in our study. The age and racial/ethnic composition of study participants varied somewhat throughout the study period with a lower proportion of samples collected from non-Hispanic whites during the first two years than during later years, reflecting the effort during these early years to target the sampling collection of nonwhites. By way of apparent happenstance, a disproportionate number of samples were collected from study participants in the oldest age category during the earlier years of the study compared to later years.

The distribution of PFAS concentrations is presented in Table 2. Most compounds were detected in over 90% of study participants. Median serum levels were highest for PFOS, followed by PFOA and PFHxS. PFOS was the predominant PFAS, comprising, on average, approximately half of the total PFAS measured in sera, followed by PFOA, PFHxS, and PFNA. The remaining six compounds combined contributed to less than 10% of the total PFAS measured. PFAS profiles appeared similar for each year of blood sample collection (data not shown).

To assess the degree to which the serum PFAS concentrations in our study population are representative of the general U.S. population, we compared the geometric mean serum PFAS concentrations in our study to those reported in NHANES participants for contemporaneous time periods (i.e., 2011–2012 and 2013–2014). These comparisons were restricted to non-Hispanic white women over the age of 40 and limited to only the six PFASs with detection frequencies greater than 65% in both populations (Figure S1, in the Supporting Information). Serum concentrations of PFNA and PFHxS in our study were generally similar to those in NHANES participants. Concentrations in our study population, however, were notably higher for PFDA and MeFOSAA and lower for PFOA and PFOS.

Spearman Rank correlations between all PFASs were statistically significant ($p < 0.05$), with positive correlation coefficients, (r) ranging from 0.07 to 0.76 (Supporting Information, Table S1). PFOS and PFOA were strongly correlated ($r = 0.61$). Additionally, PFOS was strongly correlated with PFHxS ($r = 0.61$) and PFNA ($r = 0.59$). PFOA was strongly correlated with PFNA ($r = 0.67$) and PFDA ($r = 0.59$). PFNA was most strongly correlated with PFDA ($r = 0.76$). EtFOSAA and MeFOSAA generally were not strongly correlated with other compounds, other than with PFOS and PFOSA. EtFOSAA and MeFOSAA, as the degradation intermediates of N-ethyl perfluorooctanesulfonamidoethanol (EtFOSE) and N-methyl perfluorooctanesulfonamidoethanol (MeFOSE), have been observed to undergo biotransformation to yield PFOSA and PFOS.^{1,45}

Temporal trends in serum PFAS concentrations are presented in Figure 1 and Table 3. A downward trend towards lower levels in more recently collected samples was evident for all PFASs (Figure 1), although the slope of the decline varied considerably by compound. Declining trends generally persisted after adjustment for covariates. The average annual percent changes (aAPC) in serum PFAS levels, as estimated from unadjusted and adjusted multivariable linear models, are presented in Table 3. Results from unadjusted models indicated that serum levels of all PFASs significantly declined over the period of the study. Adjustment for covariates did not substantially change the results, with the exception of PFHxS, for which the decline was diminished and no longer statistically significant (aAPC = -2.32 , $p = 0.3343$). Statistically significant adjusted declines ranged from about 9% for PFOA to approximately 19% for PFOSA.

Higher serum concentrations were statistically significantly associated with increasing participant age for all PFASs except PFNA ($p = 0.16$), PFDA ($p = 0.70$), and PFUnDA ($p = 0.40$) (data not shown). To evaluate whether temporal trends in PFAS concentrations varied by age, we conducted age-stratified regression analyses. These analyses (summarized in Figure 2) demonstrate that the downward trend in serum PFAS concentrations was generally evident in all age groups for all compounds, with the exception of PFHxS. For most compounds, the average annual declines in serum concentrations were steepest among the oldest women (age 70+).

Table 1. Characteristics of Study Participants (n = 1257)

	year of sample collection											
	all years		2011		2012		2013		2014		2015	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
age (yrs)												
40–49	76	(6)	26	(6)	30	(9)	11	(4)	7	(4)	2	(2)
50–59	180	(14)	58	(14)	52	(16)	39	(16)	19	(11)	12	(13)
60–69	501	(40)	143	(35)	134	(41)	106	(42)	73	(42)	45	(48)
70–79	377	(30)	115	(28)	84	(26)	79	(31)	70	(40)	29	(31)
80+	123	(10)	69	(17)	27	(8)	16	(6)	6	(3)	5	(5)
race/ethnicity ^a												
non-Hispanic white	940	(75)	312	(76)	177	(54)	206	(82)	161	(92)	84	(90)
black	93	(7)	32	(8)	42	(13)	18	(7)	0	(0)	1	(1)
hispanic	103	(8)	35	(9)	51	(16)	11	(4)	4	(2)	2	(2)
API	95	(8)	26	(6)	56	(17)	9	(4)	3	(2)	1	(1)
other/NR	26	(2)	6	(1)	1	(0)	7	(3)	7	(4)	5	(5)
total	1,257	(100)	411	(100)	327	(100)	251	(100)	175	(100)	93	(100)

^aAPI = Asian or Pacific Islander; other/NR = other race/ethnicity or race/ethnicity not reported.

Table 2. Distributions of Serum PFAS Concentrations (ng/mL) among Study Participants (n = 1257),^a 2011–2015

		serum concentration (ng/mL)					
acronym	name	DF ^b	LOD ^c	mean	median	minimum	maximum
PFHpA	perfluoroheptanoic acid	63.6	0.033	0.084	0.042	0.011	1.160
PFOA	perfluorooctanoic acid	99.9	0.108	2.996	2.470	0.096	27.600
PFNA	perfluorononanoic acid	99.2	0.036	1.070	0.909	0.017	10.400
PFDA	perfluorodecanoic acid	90.1	0.048	0.279	0.221	0.022	3.910
PFUnDA	perfluoroundecanoic acid	96.5	0.018	0.170	0.134	0.007	1.310
PFHxS	perfluorohexane sulfonic acid	99.9	0.017	2.231	1.580	0.011	21.800
PFOS	perfluorooctane sulfonic acid	99.6	0.080	8.539	7.070	0.047	99.800
PFOSA	perfluorooctane sulfonamide	74.5	0.017	0.075	0.039	0.001	1.240
EtFOSAA	2-(<i>N</i> -ethyl-perfluorooctane sulfonamido) acetic acid	76.4	0.014	0.064	0.031	0.004	1.360
MeFOSAA	2-(<i>N</i> -methyl-perfluorooctane sulfonamido) acetic acid	96.4	0.017	0.378	0.195	0.006	9.200

^aAssay data missing for PFNA ($n = 9$) and PFOSA ($n = 83$) due to laboratory failure. ^bDF = detection frequency. ^cLOD = average level of detection.

Table 3. Estimated Average Annual Percent Change (aAPC) in Serum PFAS Levels, 2011–2015: Results from Unadjusted and Multivariable Adjusted Linear Regression Models

compound	time trend variable ^b	unadjusted					adjusted ^a				
		β^c	s.e. (β)	p value	model r^2	aAPC	β^c	s.e. (β)	p value	model r^2	aAPC
PFHpA	time-years	-0.2826	0.0396	<0.0001	0.069	-10.70 ^d	-0.2752	0.0535	<0.0001	0.146	-10.60 ^d
	time-years ²	0.0467	0.0085	<0.0001			0.0453	0.0122	0.0002		
PFOA	time-years	-0.0349	0.0062	<0.0001	0.024	-7.72	-0.0423	0.0084	<0.0001	0.112	-9.28
PFNA	time-years	0.0201	0.0294	0.4938	0.077	-15.50 ^d	0.0073	0.0310	0.8145	0.148	-15.50 ^d
	time-years ²	-0.0187	0.0063	0.0032			-0.0161	0.0073	0.0283		
PFDA	time-years	0.2327	0.0354	<0.0001	0.106	-20.30 ^d	0.2662	0.0405	<0.0001	0.188	-16.50 ^d
	time-years ²	-0.0663	0.0076	<0.0001			-0.0689	0.0091	<0.0001		
PFUnDA	time-years	-0.0535	0.0086	<0.0001	0.030	-11.60	-0.0467	0.0091	<0.0001	0.230	-10.20
PFHxS	time-years	-0.0224	0.0078	0.0041	0.007	-5.03	-0.0102	0.0106	0.3343	0.188	-2.32
PFOS	time-years	-0.0422	0.0077	<0.0001	0.023	-9.26	-0.0486	0.0099	<0.0001	0.126	-10.60
PFOSA	time-years	-0.0974	0.0120	<0.0001	0.053	-20.10	-0.0911	0.0135	<0.0001	0.184	-18.90
EtFOSAA	time-years	-0.0665	0.0100	<0.0001	0.034	-14.20	-0.0850	0.0138	<0.0001	0.168	-17.80
MeFOSAA	time-years	-0.0992	0.0108	<0.0001	0.063	-20.40	-0.0832	0.0141	<0.0001	0.150	-17.40

^aPFHpA adjusted for body mass index (BMI, kg/m²), alcohol consumption, year home was built, percent of home that is carpeted, dietary salad/wine pattern, SES, urbanization, PFAS detection in drinking water, level of detection (LOD); PFOA adjusted for change in weight, menopausal status, dietary high carbohydrate pattern, socioeconomic status (SES), PFAS detection in drinking water; PFNA adjusted for race/ethnicity, physical activity, alcohol consumption, menopausal status, dietary consumption of meat, chicken/turkey, milk, eggs, fish and protein, SES, PFAS detection in drinking water; PFDA adjusted for alcohol consumption, smoking status, menopausal status, season of blood collection, dietary consumption of meat, chicken/turkey, milk, eggs, fish and protein, SES, PFAS detection in drinking water, LOD; PFUnDA adjusted for age (continuous), race/ethnicity, birthplace, BMI, alcohol consumption, age (continuous) at menopause, dietary consumption of meat, chicken/turkey, milk, eggs, fish and protein, dietary salad/wine pattern, SES; PFHxS adjusted for age (continuous), age (continuous) at menopause, season of blood collection, percent of home that is carpeted, dietary consumption of meat, chicken/turkey, milk, eggs, fish and protein, dietary salad/wine pattern, SES, urbanization, PFAS detection in drinking water; PFOS adjusted for age (continuous), race/ethnicity, menopausal status, dietary consumption of meat, chicken/turkey, milk, eggs, fish and protein, PFAS detection in drinking water; PFOSA adjusted for age (continuous), race/ethnicity, BMI, change in weight, season of blood collection, year home was built, percent of home that is carpeted, urbanization, LOD; EtFOSAA adjusted for age (continuous), race/ethnicity, pregnancy history, season of blood collection, year home was built, percent of home that is carpeted, dietary protein/fat pattern, PFAS detection in drinking water, LOD; MeFOSAA adjusted for age (continuous), race/ethnicity, year home was built, percent of home that is carpeted, fingernail biting, PFAS detection in drinking water. ^bTime-years = a real number representing the number of years and fraction of years between blood sample collection date and January 1, 2011. ^c β = regression coefficient of time trend variables from linear regression models. ^daAPC calculated from beta-coefficients of time-years and time-years², as described in Statistical Analysis Section.

■ DISCUSSION

All of the compounds reported on in this paper have been included in at least one regulatory or voluntary phase out initiative. The 3M 2002 voluntary phase out included all perfluorooctane sulfonyl fluoride (POSF)-based compounds. This covered PFOS, PFOA, and PFOS-related products and included all long chain PFAAs, including PFHxS and related precursor compounds.²⁰ While EtFOSAA and MeFOSAA are not directly included in the 3M phase-out, because they are transformation products of POSF-based products,^{1,4,5} they would be indirectly affected by this initiative. PFOS and its salts were further restricted by their addition to the Stockholm Convention in 2009,²² although the manufacturing phase-out is gradual and includes a number of exceptions for specific applications. Both the 2006 US EPA Stewardship Program and the 2006 EU restrictions targeted the long-chain perfluoroalkyl carboxylic acids (PFCAs). The US EPA program encompasses all long-chain PFCAs examined in our study (including PFHpA, PFOA, PFNA, PFDA, and PFUnDA),^{23,24} while the EU restrictions do not cover PFNA and PFHpA.²¹ As discussed in our Introduction, ongoing exposures could be continuing for a variety of reasons, despite these phase-outs.

Our findings suggest that the phase-out of the long-chain PFAAs that began during the early part of this century is reflected in declining exposures in our population of middle-aged and older California women. Serum concentrations of nearly all PFASs declined on average by 10–20% per year during the approximate four-year observation period of our study, which began approximately five to ten years after many of these compounds were phased out of use. The one notable exception was PFHxS for which levels did not show a meaningful decline over the study period. For most PFASs, older women had higher serum concentrations but greater declines than younger women.

Our findings are consistent with a large body of data that demonstrate declining serum levels of PFOS and PFOA, starting in the early 2000s.^{2,28,30,31,33–45,58–62} Such observations generally have been interpreted as evidence for reduced human exposures in response to the phase-outs of the long-chain PFASs earlier this century.^{7,13,36} Evidence for declining exposures to the other long chain PFASs is more mixed, with some studies suggesting declining serum levels,^{30,33–35,39,40,42,43,60,61} while others have suggested continuing increases or no changes in serum levels for some of these compounds.^{28,31,33,35–39,42,63} Our study, which focuses on a more recent time period than many of these earlier studies, suggests that exposures to several of the other long-chain PFAS may now be similarly declining, with the possible exception of PFHxS.

While a number of studies indicate declines in PFHxS,^{28,30,33,39,40,42,43} our findings are consistent with some reports of no change or even increases in PFHxS serum levels during recent years.^{35,36,44,45,58–61,63,64} The most likely explanation for the lack of the decline in PFHxS would be that it is a reflection of its longer bioelimination half-life compared to some of the other long-chain PFAAs. The bioelimination half-life commonly cited for PFHxS is 8.5 years compared to 5.4 years and 3.8 years for PFOS and PFOA, respectively.²⁵ Thus, the steeper declines we observed for PFOS and PFOA compared to PFHxS are generally consistent with these relative bioelimination half-lives. Furthermore, with an estimated aAPC of –2.33 years, the population halving time of PFHxS in our study would be approximately 21 years, considerably longer than the widely cited bioelimination half-life of 8.5 years.²⁵ This suggests that the bioelimination half-life of PFHxS may be longer than previously thought, a conjecture supported by emerging evidence of a longer half-life for PFHxS from other studies.^{19,61}

Figure 1. Serum concentrations (ng/mL) versus date of blood collection among 1257 California women, May 9, 2011 through August 24, 2015. Red line = fitted values from unadjusted linear regression models.

Figure 2. Average annual percent change (aAPC) of PFAS concentrations in serum collected 2011–2015 among 1257 study participants, by age group, estimated from linear regression models, adjusting for race and age (in years). Age groups chosen in order to ensure ample numbers of participants across sample years (see Table 1 for details of numbers of participants by age group and year of sample collection). * denotes that aAPC is statistically significant at $p \leq 0.05$.

Alternatively, a longer than expected population halving time, coupled with a lack of a statistically significant decline, might suggest that PFHxS exposures have not ceased despite the phaseouts. In contrast, the population halving time for PFOS in our study was 4.7 years, less than the bioelimination half-life of 5.4 years, suggesting that exposures to PFOS may be diminishing.

As discussed in our Introduction, there are numerous potential avenues for ongoing exposures. Although our understanding of the use and occurrence of precursor compounds and their contributions to the levels of PFASs in environmental and biologic media is not fully understood,^{13,34,65} exposures could be continuing indirectly through the biodegradation of precursor compounds that are still in use and degrade to PFHxS. For example, PHxSF (perfluorohexane sulfonyl fluoride) chemicals, such as perfluorohexane sulfonamide amines were identified in certain ECF (electrochemical fluorination)-based AFFF (aqueous film-forming foams) formulations, and these compounds are known PFHxS precursors.⁶⁶

It also is possible that exposures are continuing through the existing reservoir of consumer goods that were treated with PFHxS before the phase-out but are still in use today. For

example, PFHxS was widely used in commercial formulations such as Scotchgard to treat carpets and upholstered furniture. Such items may not be disposed of as frequently as other consumer products such as nonstick cookware and water-proof clothing that were more commonly treated with other PFAAs. While PFOS was generally the primary constituent of Scotchgard, formulations varied and some apparently contained very high levels of PFHxS.⁶⁷ Furthermore, studies of dust samples obtained from vacuum cleaner bags have identified carpets as a significant source of indoor PFHxS exposures.⁶⁷⁻⁶⁹ In our study, serum levels of PFHxS were associated with more carpeting in the home, and in our regression models, controlling for the percent of flooring that was covered with home carpeting reduced the magnitude and statistical significance of the temporal trend in PFHxS.

Routes of human PFAS exposures have not been fully elucidated and are particularly poorly understood for the PFASs other than PFOA and PFOS. Food and water contamination, however, are often cited as the two primary routes of human exposures, followed by ingestion and inhalation of dust.^{2,3,70} Two recent temporal analyses of PFASs that failed to observe declines in PFHxS (one reporting increases in serum PFHxS⁵⁹ and the other reporting no significant changes in serum PFHxS levels⁶¹), attributed their findings to ongoing known exposures through contaminated drinking water. While our study population did not have any known PFAS drinking water contamination, we were able to assign crude indicators of possible drinking water contamination based on detectable PFASs contained in the US EPA's Unregulated Contaminant Monitoring Rule (UCMR3) data.⁷¹ This approach, described in detail elsewhere,⁵³ however, was hampered by the UCMR3 data's high limits of detection and the need to rely on zip codes to imperfectly link the participants' residences to the UCMR3 data, resulting in substantial uncertainties in exposure classification.⁵³ While only 5% of our study population had detectable levels of PFASs in drinking water, in our multivariable regression models these indicators were predictors of serum concentrations for several of the PFASs we evaluated, including PFHxS. However, when we removed the individuals with PFAS detected in their drinking water from our temporal analyses reported here, our results did not markedly change; there continued to be no statistically significant decline in PFHxS serum levels among women with no detectable PFAS in drinking water (data not shown). This seems to suggest that ongoing exposures via drinking water do not explain the lack of a temporal decline in PFHxS. However, given the limitations of our exposure assessment method we cannot fully discount the possibility that PFHxS exposures could be continuing through contaminated drinking water.

Our observation of higher levels of most PFASs with increasing age adds to a growing, although not entirely consistent, body of literature that suggests serum levels increase with age among adults.^{6,28,29,33,36,44,60,63,72-74} This is likely due to greater historical opportunity of PFAS exposures among older people during earlier time periods when consumer products were more widely treated with PFASs prior to the long chain phaseouts. The relationship between age and serum PFAS concentrations, however, was not observed for all of the PFASs measured in our study. The three PFASs for which there was no relationship with age (PFNA, PFDA, and PFUnDA) are all longer chain PFAS and likely to have long half-lives so one would expect increasing levels with age. The fact that we do not see such a relationship might suggest that within the age range of our participants (i.e, middle-aged and older adults) the historical opportunities for exposure among our study participants were somewhat uniform across the age groups included in our study. Unfortunately, we do not know enough about the exposure routes for these specific PFASs to be able to meaningfully speculate further on this finding.

The generally greater proportionate declines in serum levels observed among the oldest compared to the youngest women in our study are noteworthy and warrant further investigation. These age-related differences in temporal declines in serum concentrations may reflect varying exposures due to age-related differences in such behavioral factors as dietary habits, use of PFAS-treated consumer goods, and indoor–outdoor activity patterns. Alternatively, they could reflect age-related differences in the rate of uptake, metabolism, or excretion of PFASs. While we lack a full understanding of how the pharmacokinetics of these compounds may change with age, there is some evidence indicating that the bioelimination half-lives may be considerably shorter among younger compared to older women.¹⁹ It has been suggested that such age-related differences in bioelimination rates are due to premenopausal women excreting PFAS through menstrual bleeding and lactation,¹⁹ but our study population is comprised almost entirely (91%) of postmenopausal women. This would be an interesting area of future inquiry.

The analyses presented here were part of a preliminary descriptive analysis conducted as a prelude to our breast cancer case-control study. Since the data were not specifically collected for the purpose of the current analyses, a number of limitations are worth noting. Ideally, a temporal trend analysis would have repeated measurements in individuals over time rather than cross-sectional measurements covering an approximate 4-year time period as we had in this study. Although we adjusted for temporal differences in a number of factors that may be related to serum PFAS levels, information on these factors was not collected in a fashion ideally suited to the current analyses. The explanatory power of our regression models, with R^2 values all below 0.25, indicates that substantial variability in PFAS levels was not captured by our analyses. A better understanding of the determinants of exposure is critical to our understanding of the degree to which exposures are continuing and is key to mitigating such exposures.

Our study population was derived from the CTS which is comprised of predominantly non-Hispanic white professional women. The degree to which our results may extend to the general population is somewhat difficult to ascertain. Our comparison of the geometric means of PFAS concentrations in our study to those reported in a similar subset of NHANES participants (Figure S1), suggested some notable differences. Such differences may reflect geographic differences in exposure (our participants are all from California) or may be due to the slightly different age structure of the two populations (NHANES contains comparatively higher proportions of women in both the oldest age (80+ years) and youngest age (40–49 years) categories than in our study, as detailed in the Supporting Information, Table S2).

It also should be noted that the time period covered by our study is somewhat narrow (4.25 years) and does not encompass the period before these compounds began to be phased out. Consequently, our study cannot directly assess the degree to which levels are declining due to regulatory and voluntary measures aimed at reducing exposures.

Despite these limitations, this study offers a number of strengths. As one of the largest population-based studies conducted to date, it provides precise estimates of serum PFAS levels in a population of middle-aged and older women, a population that has been largely overlooked in other studies. Most temporal assessments of PFAS biomonitoring data have been conducted in populations with heavy exposures due to known environmental contamination from large industrial releases of PFASs, occupational cohorts, or from samples collected from younger women of childbearing age. Our results are unique in providing insights into temporal trends in potential PFAS exposures among a segment of the general population who is not known to have unusual or heavy PFASs exposures.

In conclusion, our results suggest that the phase-out of the long-chain PFAs and some of their associated precursors has resulted in substantial reductions in human exposures, at least to several of the most commonly measured long-chain PFASs. The degree to which such declines may extend to men, people of color, younger adult populations, and children is beyond the scope of the present study. Furthermore, the exposure profiles of the more than 3000 PFASs currently in use are complex, poorly understood, and complicated by the ability of some PFASs to degrade and biotransform into other PFAS compounds. The fact that most of the compounds we measured were detected in over 90% of participants nearly a decade after being phased-out is testament to their persistence and should serve as a cautionary note against replacing these compounds with regrettable substitutions that may have similar toxicological properties and associated health risks.^{17,75} Our findings for PFHxS suggest that the bioelimination rate for PFHxS may be longer than what is generally thought and/or that exposures may be ongoing, underscoring the importance of continued biomonitoring and research efforts to elucidate current pathways of exposure.

■ ASSOCIATED CONTENT

*S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.7b04650.

Laboratory Methods: Serum PFASs Measurements. Table S1. Spearman Rank Correlation Coefficients between PFAS compounds measured in sera of study participants (n = 1,257), 2011–2015. Table S2. Age distribution of study participants (CTS) and National Health and Nutrition Examination Survey (NHANES) participants included in Figure S1 (restricted to non-Hispanic white women age ≥ 40 years). Figure S1. Geometric means and 95% confidence intervals (95% CIs) of serum PFAS concentrations for participants in this study (CTS) versus National Health and Nutrition Examination Survey (NHANES) participants for blood samples collected in 2011–2012 and 2013–2014. (PDF)

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