



## Original Contribution

# Perfluoroalkyl Chemicals and Chronic Kidney Disease in US Adults

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Chronic kidney disease (CKD) is a major public health problem. Identifying novel risk factors for CKD, including widely prevalent environmental exposures, is therefore important. Perfluoroalkyl chemicals (PFCs), including perfluorooctanoic acid and perfluorooctane sulfonate, are manmade chemicals that have been detected in the blood of more than 98% of the US population. Results from experimental animal studies have suggested that an association between PFCs and CKD is plausible. However, in humans, the relation between serum PFCs and CKD has not been examined. The authors examined the relation of serum PFCs and CKD in 4,587 adult participants (51.1% women) from the combined 1999–2000 and 2003–2008 cycles of the National Health and Nutritional Examination Survey for whom PFC measurements were available. The main outcome was CKD, defined as a glomerular filtration rate of less than 60 mL/minute/1.73 m<sup>2</sup>. The authors found that serum levels of PFCs, including perfluorooctanoic acid and perfluorooctane sulfonate, were positively associated with CKD. This association was independent of confounders such as age, sex, race/ethnicity, body mass index, diabetes, hypertension, and serum cholesterol level. Compared with subjects in quartile 1 (referent), the multivariable odds ratio for CKD among subjects in quartile 4 was 1.73 (95% confidence interval: 1.04, 2.88; *P* for trend = 0.015) for perfluorooctanoic acid and 1.82 (95% confidence interval: 1.01, 3.27; *P* for trend = 0.019) for perfluorooctane sulfonate. The present results suggest that elevated PFC levels are associated with CKD.

fluorocarbons; kidney diseases; nutrition surveys

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; PFCs, perfluoroalkyl chemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SE, standard error.

Chronic kidney disease (CKD), defined as a glomerular filtration rate of less than 60 mL/minute/1.73 m<sup>2</sup> (1, 2), is present in approximately 13.1% of the adult US population (3). CKD is a stage early in the renal disease continuum in which prevention and/or delay of irreversible kidney damage that leads to end-stage renal disease may be possible. CKD is also known to be an independent risk factor for cardiovascular disease and early death (4). In a recent study in which 2 consecutive national surveys were compared, Coresh et al. (3) reported an increase in the prevalence of CKD from 1988–1994 to 1999–2004, suggesting it to be a growing public health problem. From a public health point of view, identifying new risk factors for CKD, particularly widely available environmental exposures that have not been previously studied, is therefore important.

There is growing concern regarding human exposure to perfluoroalkyl chemicals (PFCs), including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), because these chemicals are persistent in the environment, bioaccumulated, and biomagnified along food chains and have been shown to cause developmental and other adverse health effects in laboratory animals (5, 6). PFCs have been widely used in the manufacture of industrial and consumer products such as surfactants, lubricants, polishes, paper and textile coatings, food packaging, and fire-retarding foams. PFCs have been detected in the blood of more than 98% of the US population (7). Although both PFOS and PFOA share a ubiquitous presence among both humans and wildlife, PFOS has a wider distribution that is attributed in part to its resistance to degradation in ecologic systems and its

bioconcentration (8). Recent evidence from retired employees of PFC production facilities suggests elimination half-lives of 5.4 years for PFOS and 3.8 years for PFOA (9).

Studies have suggested that the kidney serves as one of the target organs for PFCs (10). Histopathologic observations have indicated that greater concentrations of PFOS and PFOA were found in the kidneys (11, 12) because the primary route of PFC excretion is through the kidneys (13). Also, renal hypertrophy and histopathologic changes indicative of soft tissue proliferation in the renal interstitium and in renal microvascular disease were observed in rats exposed to PFCs (8). Results from in vitro studies have suggested that PFCs are associated with alterations in endothelial-cell permeability (14, 15). Alterations in renal microvascular endothelial-cell permeability are considered a central mechanism of ischemic renal failure in rat models (16–18).

In previous epidemiologic studies, both PFOA and PFOS have been linked to higher cholesterol levels in humans (19–23). Higher cholesterol levels have in turn been found to be independently associated with an increased risk of CKD (24, 25). In a recent epidemiologic study in adolescents and adults, Lin et al. (26) found that higher PFC levels were related to insulin resistance and the metabolic syndrome. Both insulin resistance and components of the metabolic syndrome have previously been shown to be associated with CKD in epidemiologic studies (27, 28). Finally, we recently found that higher PFOA and PFOS levels were associated with serum uric acid levels (29), a marker that has been shown to be associated with an increased risk of the development of hypertension (30) and CKD (31) in epidemiologic studies. Despite these leads, to our knowledge, no previous study has examined the putative association between PFCs and CKD. We therefore examined this relation in a contemporary, nationally representative sample of adults.

## MATERIALS AND METHODS

The current study was based on merged data from the 1999–2000, 2003–2004, 2005–2006, and 2007–2008 cycles of the National Health and Nutrition Examination Survey (NHANES). Detailed descriptions of the NHANES study design and methods have been published previously (32). In brief, the NHANES survey includes a stratified, multi-stage probability sample representative of the civilian non-institutionalized US population. Selection is based on counties, blocks, households, and individuals within households and includes oversampling of low-income persons, persons 60 years of age or older, African Americans, and Mexican Americans to provide stable estimates for these groups. The survey also includes biomonitoring for PFCs by the National Center for Environmental Health in a random subsample of one-third of the participants. Subjects are required to sign a consent form before participation, and approval was obtained from the Human Subjects Committee of the US Department of Health and Human Services.

The present study sample consisted of 5,717 NHANES participants 20 years of age or older for whom PFC measurements were available. We further excluded subjects with

self-reported cardiovascular disease ( $n = 572$ ) or missing data ( $n = 558$ ) on serum creatinine or covariates included in the multivariable model, including educational level, body mass index (BMI), and cholesterol levels. This resulted in 4,587 participants (51.1% women).

## Main outcome of interest: CKD

In NHANES 1999–2000, serum creatinine measurements were performed at the Coulston Foundation Laboratory (Boston, Massachusetts) using a Roche Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Indiana; kinetic alkaline picrate) (33). We used the following Deming regression equation provided by Selvin et al. (34) in a calibration substudy to standardize NHANES 1999–2000 serum creatinine levels: standard creatinine =  $0.147 + 1.013 \times$  (NHANES 1999–2000 uncalibrated serum creatinine).

In NHANES 2003–2006, serum creatinine measurements were performed at Collaborative Laboratory Services (Ottumwa, Iowa) using the Beckman Coulter Synchron LX20 (Beckman Coulter, Fullerton, California; kinetic alkaline picrate) (35, 36). We did not correct the NHANES 2003–2004 serum creatinine values as recommended by the calibration study (34). However, we applied the following equation to standardize NHANES 2005–2006 serum creatinine levels as recommended by the National Center for Health Statistics on the basis of their calibration study (36): standard creatinine =  $-0.016 + 0.978 \times$  (NHANES 2005–2006 uncalibrated serum creatinine).

In NHANES 2007–2008, serum creatinine measurements were performed at Collaborative Laboratory Services. In 2007, creatinine was measured using the Beckman Coulter Synchron LX20 and not standardized according to National Kidney Disease Educational Program guidelines (37). On the basis of the recommendation by the National Center for Health Statistics, NHANES 2007 serum creatinine values were reduced by 0.08 mg/dL to convert them to standardized creatinine values. In 2008, serum creatinine measurements were performed using the Beckman Coulter UniCel Dx800 Synchron Clinical System and were standardized according to National Kidney Disease Educational Program guidelines.

Estimated glomerular filtration rate (eGFR) was determined from serum creatinine values by using the 4-variable Modification of Diet in Renal Disease study equation (38), as follows:  $eGFR = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ . CKD was defined as an eGFR of less than 60 mL/minute/1.73 m<sup>2</sup>, consistent with the definitions of the National Kidney Foundation Kidney Disease Outcome Quality Initiative (1) working group and the Kidney Disease: Improving Global Outcomes position statement (2).

## Exposure measurements

Age, sex, race/ethnicity, smoking status, alcohol intake (g/day), level of education, history of diabetes, oral hypoglycemic medication intake, insulin administration, and antihypertensive medication use were assessed using a questionnaire. Individuals who had not smoked 100 cigarettes or more in

**Table 1.** Characteristics of the Study Population, by Category of Plasma Perfluoroalkyl Chemical Level, National Health and Nutrition Examination Survey, 1999–2008

Characteristic	Perfluorooctanoic Acid <sup>a</sup>			Perfluorooctane Sulfonate <sup>b</sup>				
	Quartile 1		Quartile 4	Quartile 1		Quartile 4	P Value	
	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)		
Age, years		43.0 (0.7)	45.0 (0.5)	0.018		40.6 (0.6)	45.3 (0.6)	<0.0001
Female sex	71.1		47.1	<0.0001	73.0		39.5	<0.0001
Race/ethnicity								
Non-Hispanic white	61.9		76.6	<0.0001	67.1		74.8	0.0043
Non-Hispanic black	13.4		8.8	0.0004	7.9		11.1	0.0006
Mexican-American or other	24.7		14.6	<0.0001	25.0		14.2	<0.0001
Educational level								
Less than high school	23.8		16.3	<0.0001	23.1		13.4	0.0002
High school graduate	24.0		25.7	0.71	22.4		27.2	0.059
Postsecondary education	52.3		58.0	0.0016	54.6		59.5	0.067
Smoking status								
Never smoker	57.1		52.2	0.0002	53.7		50.6	0.19
Former smoker	21.6		23.3	0.24	19.8		24.0	0.0005
Current smoker	21.2		24.6	0.0037	26.5		25.4	0.035
Alcohol intake								
Nondrinker	37.0		28.8	<0.0001	34.8		29.8	0.45
Moderate drinker	43.4		43.1	0.74	41.5		40.3	0.17
Heavy drinker	19.6		28.1	<0.0001	23.7		29.9	0.23
Body mass index <sup>c</sup>		28.2 (0.3)	28.5 (0.3)	0.78		28.3 (0.3)	28.3 (0.3)	0.99
Diabetes mellitus	10.5		7.8	0.067	8.1		7.1	0.10
Systolic blood pressure, mm Hg		118.6 (0.6)	121.7 (0.7)	<0.0001		117.8 (0.6)	122.6 (0.6)	<0.0001
Diastolic blood pressure, mm Hg		69.8 (0.4)	71.9 (0.6)	<0.0001		69.9 (0.4)	71.6 (0.5)	0.001
Total cholesterol, mg/dL		194.7 (1.7)	199.4 (1.4)	0.0005		194.4 (1.6)	203.8 (1.6)	<0.0001
Estimated glomerular filtration rate, mL/minute/1.73 m <sup>2</sup>		93.0 (1.1)	86.8 (0.8)	<0.0001		94.2 (1.1)	85.4 (0.7)	<0.0001
Chronic kidney disease <sup>d</sup>	4.9		6.4	0.026	3.7		6.9	<0.0001
Uric acid, mg/dL		4.8 (0.1)	5.5 (0.1)	<0.0001		5.0 (0.1)	5.6 (0.1)	<0.0001
Glycohemoglobin		5.5 (0.04)	5.5 (0.03)	0.20		5.4 (0.04)	5.5 (0.02)	0.0083
C-reactive protein, mg/dL		0.4 (0.04)	0.4 (0.02)	0.10		0.5 (0.04)	0.3 (0.02)	0.0006

Abbreviation: SE, standard error.

<sup>a</sup> Perfluorooctanoic acid quartiles: quartile 1, <2.8 ng/mL; quartile 2, 2.8–4.1 ng/mL; quartile 3, 4.2–5.9 ng/mL; and quartile 4, >5.9 ng/mL.

<sup>b</sup> Perfluorooctane sulfonate quartiles: quartile 1, <11.7 ng/mL; quartile 2, 11.7–18.7 ng/mL; quartile 3, 18.8–29.5 ng/mL; and quartile 4, >29.5 ng/mL.

<sup>c</sup> Weight (kg)/height (m)<sup>2</sup>.

<sup>d</sup> Chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/minute/1.73 m<sup>2</sup>.

their lifetimes were considered to be never smokers. Those who had smoked 100 cigarettes or more in their lifetimes were considered to be former smokers if they answered in the negative to the question “Do you smoke now?” and current smokers if they answered in the affirmative. BMI was calculated as weight in kilograms divided by height in meters squared. Heavy alcohol drinking was defined as consumption of more than 2 drinks/day on average over the past 12 months.

Rigorous procedures with quality-control checks were used in blood collection; details about these procedures are avail-

able in the NHANES *Laboratory Procedures Manual* (39). PFCs were measured in serum of participants by the National Center for Environmental Health using automated solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry; details of laboratory methods have been published previously (7). Our study examined PFOA and PFOS, PFCs that have been detected in more than 98% of humans. Values below the limit of detection were reported by NHANES investigators as the limit of detection divided by the square root of 2. The

**Table 2.** Association Between Plasma Perfluoroalkyl Chemical Level and Estimated Glomerular Filtration Rate, National Health and Nutrition Examination Survey, 1999–2008

Plasma Perfluoroalkyl Chemical Level	Unweighted Sample Size (No. of Subjects)	Age- and Sex-Adjusted Mean Difference in eGFR, mL/minute/1.73 m <sup>2</sup>		Multivariable-Adjusted Mean Difference in eGFR <sup>a</sup> , mL/minute/1.73 m <sup>2</sup>	
		Mean Difference	95% CI	Mean Difference	95% CI
Perfluorooctanoic acid					
Quartile 1 (<2.8 ng/mL)	1,176	0	Referent	0	Referent
Quartile 2 (2.8–4.1 ng/mL)	1,141	–3.5	–5.2, –1.8	–2.6	–4.3, –0.9
Quartile 3 (4.2–5.9 ng/mL)	1,141	–5.2	–7.1, –3.2	–3.6	–5.6, –1.5
Quartile 4 (>5.9 ng/mL)	1,129	–7.6	–9.6, –5.6	–5.7	–7.9, –3.5
<i>P</i> for trend		<0.0001		<0.0001	
Perfluorooctane sulfonate					
Quartile 1 (<11.7 ng/mL)	1,152	0	Referent	0	Referent
Quartile 2 (11.7–18.7 ng/mL)	1,151	–2.6	–4.5, –0.7	–1.7	–3.5, 0.1
Quartile 3 (18.8–29.5 ng/mL)	1,137	–6.4	–8.3, –4.5	–4.9	–6.8, –3.2
Quartile 4 (>29.5 ng/mL)	1,147	–8.1	–10.4, –5.9	–6.7	–8.9, –4.4
<i>P</i> for trend		<0.0001		<0.0001	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

<sup>a</sup> Adjusted for age (20–44, 45–64, or >64 years), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), educational level (less than high school, high school graduate, or postsecondary education), smoking status (never, former, or current smoker), alcohol consumption (nondrinker, moderate drinker, or heavy drinker), body mass index category (normal or overweight/obese), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), diabetes (absent or present), serum total cholesterol level (in mg/dL), and glycohemoglobin (%).

limits of detection were 0.1 ng/mL for PFOA and 0.2 ng/mL for PFOS, and the interassay coefficients of variation were 11% for PFOA and 13% for PFOS (7).

Serum total cholesterol was measured enzymatically. Serum glucose was measured by using the modified hexokinase method at the University of Missouri Diabetes Diagnostic Laboratory (Columbia, Missouri). Diabetes was defined using the guidelines of the American Diabetes Association as a serum glucose level of 126 mg/dL or higher after fasting for a minimum of 8 hours, a serum glucose level of 200 mg/dL or higher after fasting less than 8 hours before an NHANES visit, a glycosylated hemoglobin value of 6.5% or more, or self-reported current use of oral hypoglycemic medication or insulin. Seated systolic and diastolic blood pressures were measured using a mercury sphygmomanometer according to the American Heart Association and Seventh Joint National Committee (40) recommendations. Up to 3 measurements were averaged for systolic and diastolic pressures. Patients were considered hypertensive if they reported current use of blood pressure-reducing medication and/or if they had a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher.

### Statistical analysis

Serum PFCs, including PFOA and PFOS, were analyzed as both a continuous variable and a categorical variable. For the analysis as a continuous variable, PFC values were log-transformed (base 2) as a result of their skewed distribution. We categorized serum PFCs into quartiles (PFOA quartiles: quartile 1 = <2.8 ng/mL, quartile 2 = 2.8–4.1 ng/mL, quartile 3 = 4.2–5.9 ng/mL, and quartile 4 = >5.9 ng/mL;

PFOS quartiles: quartile 1 = <11.7 ng/mL, quartile 2 = 11.7–18.7 ng/mL, quartile 3 = 18.8–29.5 ng/mL, and quartile 4 = >29.5 ng/mL). We fitted multivariable linear regression models to examine the association between increasing levels of serum PFCs and changes in eGFR. We then examined the consistency of the association between serum PFCs and eGFR by performing analyses stratified by age, sex, race/ethnicity, educational level, and BMI. We subsequently fitted multivariable logistic regression models to calculate the odds ratios for CKD for each increase in PFC level, using the lowest category as the referent. In these analyses, we used 2 models with progressive levels of adjustment (the age- and sex-adjusted model and the multivariable model) and additionally adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), educational level (less than high school, high school graduate, or postsecondary education), smoking status (never, former, or current smoker), alcohol consumption (nondrinker, moderate drinker, or heavy drinker), BMI category (normal or overweight/obese), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), diabetes (absent or present), serum total cholesterol level (in mg/dL), and glycohemoglobin (percent). Trends in the odds ratios for CKD across increasing serum PFC levels were determined by modeling increasing PFC categories as ordinal variables. Sample weights that accounted for the unequal probabilities of selection, oversampling, and nonresponse were applied for all analyses using SUDAAN, version 8.0 (Research Triangle Institute, Research Triangle Park, North Carolina) and SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Standard errors were estimated using the Taylor series linearization method.

**Table 3.** Association Between Plasma Perfluoroalkyl Chemical Level and Estimated Glomerular Filtration Rate, According to Sociodemographic Characteristics, National Health and Nutrition Examination Survey, 1999–2008

Sociodemographic Subgroup <sup>a</sup>	Multivariable-Adjusted Mean Difference in eGFR, mL/minute/1.73 m <sup>2</sup>			
	Perfluorooctanoic Acid <sup>b</sup> (Quartile 4 – Quartile 1)		Perfluorooctane Sulfonate <sup>b</sup> (Quartile 4 – Quartile 1)	
	Mean Difference	95% CI	Mean Difference	95% CI
Age, years				
<60	–6.2	–8.6, –3.8	–6.5	–9.1, –3.9
≥60	–3.9	–8.6, 0.7	–4.0	–8.1, 0.0
Sex				
Male	–4.2	–7.1, –1.3	–6.8	–10.1, –3.5
Female	–5.2	–8.1, –2.3	–5.3	–7.9, –2.6
Race/ethnicity, %				
Non-Hispanic white	–4.2	–6.6, –1.7	–6.6	–9.7, –3.8
Non-Hispanic black	–5.6	–10.3, –0.8	–7.1	–13.9, –0.3
Mexican-American or other	–7.6	–13.5, –1.7	–7.0	–11.9, –1.2
Educational level, %				
Less than high school	–9.0	–13.9, –4.1	–6.4	–11.0, –1.7
High school graduate	–2.4	–5.6, 0.8	–5.9	–9.8, –2.0
Postsecondary education	–5.8	–9.1, –2.4	–6.7	–9.5, –3.8
Body mass index <sup>c</sup>				
<30	–5.3	–7.8, –2.8	–6.9	–9.6, –4.3
≥30	–6.4	–9.8, –3.1	–5.4	–9.6, –1.1

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

<sup>a</sup> *P* for interaction > 0.05 in all subgroup analyses.

<sup>b</sup> Adjusted for age (20–44, 45–64, or >64 years), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), educational level (less than high school, high school graduate, or postsecondary education), smoking status (never, former, or current smoker), alcohol consumption (nondrinker, moderate drinker, or heavy drinker), body mass index category (normal or overweight/obese), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), diabetes (absent or present), serum total cholesterol level (in mg/dL), and glycohemoglobin (%).

<sup>c</sup> Weight (kg)/height (m)<sup>2</sup>.

## RESULTS

Table 1 presents the baseline characteristics of the study population. Subjects with higher PFOA levels were more likely to be non-Hispanic whites, current smokers, and heavy drinkers, were more likely to have a postsecondary education and higher total cholesterol and uric acid levels, were less likely to be non-Hispanic blacks or Mexican Americans, and were less likely to have less than a high school education. The correlation between PFOA and PFOS was 0.48. The distributions of baseline characteristics were similar for PFOS and PFOA, except that persons with higher PFOS levels were more likely to be former smokers (and not current smokers) and to have a high school or postsecondary education, higher glycohemoglobin levels, higher uric acid levels, and lower C-reactive protein levels. Also, subjects with higher PFOA levels had lower mean eGFR levels and higher prevalences of CKD.

Table 2 presents the mean change in eGFR associated with increasing levels of PFC, including PFOA and PFOS. Overall, we found that increasing levels of both PFOA and PFOS were

inversely associated with eGFR levels in both the age- and sex-adjusted model and the multivariable-adjusted model.

Table 3 presents the mean change in eGFR when comparing the highest quartiles of PFOA and PFOS with the lowest within subgroups stratified by age, sex, race/ethnicity, BMI, and educational level. Consistent with the findings for the whole cohort, we found that overall higher PFOA and PFOS levels were inversely associated with eGFR levels within these stratified subgroups (*P* for interaction > 0.05 in all subgroup analyses).

Table 4 presents the odds ratios for CKD associated with increasing levels of PFOA and PFOS in the whole population. We found that both PFOA and PFOS were positively associated with CKD in the age- and sex-adjusted model and the multivariable-adjusted model.

We also performed several supplementary analyses. First, to examine whether the observed association between PFCs and CKD was explained by changes in systemic inflammation or high uric acid levels, we additionally adjusted for serum high-sensitivity C-reactive protein levels and uric acid levels in the multivariable-adjusted model in Table 4;

**Table 4.** Association Between Plasma Perfluoroalkyl Chemical Level and Chronic Kidney Disease, National Health and Nutrition Examination Survey, 1999–2008

Plasma Perfluoroalkyl Chemical Level	Unweighted Sample Size (No. of Subjects)	Chronic Kidney Disease, Weighted %	Age- and Sex-Adjusted Odds Ratio		Multivariable-Adjusted Odds Ratio <sup>a</sup>		
			OR	95% CI	OR	95% CI	
Perfluorooctanoic acid							
Quartile 1 (<2.8 ng/mL)	1,176	4.9	1	Referent	1	Referent	
Quartile 2 (2.8–4.1 ng/mL)	1,141	4.8	0.89	0.61, 1.31	0.83	0.55, 1.24	
Quartile 3 (4.2–5.9 ng/mL)	1,141	6.4	1.27	0.77, 2.10	1.24	0.75, 2.05	
Quartile 4 (>5.9 ng/mL)	1,129	7.7	1.74	1.06, 2.84	1.73	1.04, 2.88	
<i>P</i> for trend				0.013		0.015	
Perfluorooctane sulfonate							
Quartile 1 (<11.7 ng/mL)	1,152	3.7	1	Referent	1	Referent	
Quartile 2 (11.7–18.7 ng/mL)	1,151	4.7	1.13	0.63, 2.03	1.12	0.64, 1.99	
Quartile 3 (18.8–29.5 ng/mL)	1,137	6.9	1.55	0.87, 2.75	1.53	0.87, 2.67	
Quartile 4 (>29.5 ng/mL)	1,147	9.3	1.83	1.02, 3.28	1.82	1.01, 3.27	
<i>P</i> for trend				0.016		0.019	

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup> Adjusted for age (20–44, 45–64, or >64 years), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), educational level (less than high school, high school graduate, or postsecondary education), smoking status (never, former, or current smoker), alcohol consumption (nondrinker, moderate drinker, or heavy drinker), body mass index category (normal or overweight/obese), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), diabetes (absent or present), serum total cholesterol level (in mg/dL), and glycohemoglobin (%).

the association was attenuated but remained significant. Second, we examined the association between PFOA and CKD after additionally adjusting for PFOS in the multivariable model; the results were found to be similar. Third, in a sensitivity analysis to examine whether the observed inverse association between PFCs and eGFR was due to reverse causality, we performed a multivariable linear regression analysis to examine the association between eGFR and PFOA and PFOS separately among persons with and without CKD, defined as an eGFR less than 60 mL/minute/1.73 m<sup>2</sup>. For PFOA, the multivariable-adjusted beta coefficient was –1.6 (standard error (SE), 0.8) among those with CKD and –2.8 (SE, 0.6) among those without CKD (*P* < 0.05 for both betas). For PFOS, the multivariable-adjusted beta coefficient was –1.8 (SE, 0.8) among those with CKD and –3.2 (SE, 0.6) among those without CKD (*P* < 0.05 for both betas).

## DISCUSSION

In a representative sample of US adults, we found that higher PFOA and PFOS levels were positively associated with CKD. This association appeared to be independent of traditional confounders such as age, sex, race/ethnicity, smoking status, heavy alcohol intake, BMI, diabetes, hypertension, and serum cholesterol levels. Our results contribute to the emerging data (19, 20, 29) on the health effects of PFCs, suggesting for the first time that PFOA and PFOS are potentially related to CKD. However, because of the cross-sectional nature of the current study, we cannot exclude the possibility of reverse causality.

The PFCs are a family of synthetic, highly stable perfluorinated compounds with a wide range of uses in industrial

and consumer products, from stain- and water-resistant coatings for carpets and fabrics to fast-food contact materials, fire-resistant foams, paints, and hydraulic fluids (5). The carbon-fluoride bonds that characterize PFCs and make them useful as surfactants are highly stable, and recent reports have indicated the widespread persistence of certain PFCs in the environment and in wildlife and human populations globally (5, 6). The 8-carbon-chain PFOAs and PFOSs are 2 of the PFCs of most concern. They bind to serum proteins and have relatively long half-lives in serum (9). General population studies have shown that in addition to being nearly ubiquitous in blood, PFOA and PFOS may also be present in breast milk, seminal fluid, and umbilical cord blood (6).

Several lines of recent evidence have suggested that an association between PFOA and PFOS and CKD may be plausible, including evidence for renal hypertrophy and histopathologic changes indicative of soft tissue proliferation in the renal interstitium and renal microvascular disease in rats exposed to PFCs (8) and the effect of PFCs in increasing endothelial cell permeability (14, 15), which is a mechanism of renal injury in rat models of ischemic renal failure (16–18). Also, in previous epidemiologic studies, PFC levels have been shown to be associated with dyslipidemia (19–23), insulin resistance, and components of the metabolic syndrome (26), as well as high levels of serum uric acid (29), all of which have in turn been reported to be associated with the risk of developing CKD (24, 25, 27, 28, 31). In the present study, we found that higher PFC levels were positively associated with CKD. However, there have been no previous studies for comparison. The magnitude of the observed association between PFCs and CKD in

the present study, its persistence even after multivariable adjustment for confounders, and its consistency in subgroup analyses by sex and BMI suggest that these findings are less likely to be due to chance. Even though PFOS is considered to be more biologically active than PFOA (6), in the present study, we found that both PFOS and PFOA were equally associated with CKD.

Our findings are of public health importance because serum PFCs appear to be positively related to kidney disease even at relatively low background exposure levels in the US general population. Therefore, if our findings are replicated in future prospective studies, the population attributable risk of CKD by PFC exposure would be high. This is unlike findings from certain other specific populations (41) that were exposed to very high serum PFC levels through local environmental contamination. Also, because all PFCs are manmade, it may be possible to remove this excess exposure risk.

The main strengths of our study included its population-based nature, the inclusion of a representative multiethnic sample, the adequate sample size, and the availability of data on confounders for multivariable adjustment. Also, we calibrated our creatinine values to the standard creatinine measurement methods following published recommendations (34). Furthermore, all data were collected following rigorous methodology, including a study protocol with standardized quality-control checks.

The main limitation of our study was the cross-sectional nature of NHANES. Therefore, the temporal nature of the association between PFCs and kidney disease could not be determined from the present study. In CKD, when eGFR is reduced, the total filtration of PFOA and PFOS will also be reduced. That could lead to higher concentrations of these molecules in the blood and therefore an observed positive association between PFCs and CKD. An argument against reverse causality is that in a sensitivity analysis, we found that the inverse relation between PFCs and eGFR was stronger, not weaker, among persons without CKD. However, an association between PFCs and CKD due to reverse causation could also be important from a clinical and/or public health point of view because if subjects with CKD retain these compounds, the toxicities of PFCs on the kidneys or other organs (19, 20, 29) could be accentuated among CKD subjects. Finally, the definition of CKD in the present study differed from that of the National Kidney Foundation (1) in that it excluded kidney damage (no data on albuminuria) and was limited to 1 visit (no measure of chronicity). Stages 1 and 2 of CKD were not considered in our study, as data on albuminuria were not included.

In summary, in a nationally representative sample of US adults, we found that higher PFOA and PFOS levels were positively associated with CKD. This association appeared to be independent of traditional confounders such as BMI, diabetes, hypertension, and elevated serum cholesterol levels. Our results contribute to the emerging literature on the health effects of PFCs by demonstrating an association with CKD, which is a growing public health problem in the United States. However, because of the cross-sectional nature of the present study, we cannot exclude the possibility of reverse causality, which implies that the mechanism for higher PFC levels in blood is lack of excretion in CKD.

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