ONLINE FIRST

Perfluorooctanoic Acid and Cardiovascular Disease in US Adults

Anoop Shankar, MD, PhD; Jie Xiao, MS; Alan Ducatman, MD, MSc

Background: Cardiovascular disease (CVD) is a major public health problem. Identifying novel risk factors for CVD, including widely prevalent environmental exposures, is therefore important. Perfluorooctanoic acid (PFOA) is a manmade chemical used in the manufacture of common household consumer products. Biomonitoring surveys have shown that PFOA is detectable in the blood of more than 98% of the US population. Experimental animal studies suggest that an association between PFOA and CVD is plausible. However, this association in humans has not been previously examined. We therefore examined the independent relationship between serum PFOA levels and CVD outcomes in a representative sample of Americans.

Methods: We examined 1216 subjects (51.2% women) from the 1999-2003 National Health and Nutritional Examination Survey. Serum PFOA levels were examined in quartiles. The main outcomes of interest were self-reported CVD, including coronary heart disease and stroke, and objectively measured peripheral arterial disease (PAD), defined as an ankle-brachial blood pressure index of less than 0.9.

Results: We found that increasing serum PFOA levels are positively associated with CVD and PAD, independent of confounders such as age, sex, race/ethnicity, smoking status, body mass index, diabetes mellitus, hypertension, and serum cholesterol level. Compared with quartile 1 (reference) of PFOA level, the multivariable odds ratio (95% CI) among subjects in quartile 4 was 2.01 (1.12-3.60; $P=.01$ for trend) for CVD and 1.78 (1.03-3.08; $P=.04$ for trend) for PAD.

Conclusion: Exposure to PFOA is associated with CVD and PAD, independent of traditional cardiovascular risk factors.

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HUMAN EXPOSURE TO PERfluorooctanoic acid (PFOA) and other perfluoroalkyl chemicals (PFCs) has raised concern 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.[1-3] Perfluorooctanoic acid has 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.[3] In addition, PFOA has been detected in the blood of more than 98% of Americans.[4] Recent evidence from retired employees in PFOA production facilities suggest a relatively long elimination half-life of approximately 3.8 years for PFOA.[5]

Cardiovascular disease (CVD) is the leading cause of death in the United States.[6] Approximately 70% of CVD can be attributed to modifiable, nongenetic factors,[7] and classic risk factors, such as smoking status and obesity, among others, do not account for all the observed CVD risk in the general population.[8,9] Recent studies have suggested that common environmental exposures affecting large sections of the population may be a determinant of CVD risk.[10,11] Because virtually all US adults have detectable blood levels of PFCs, an intriguing hypothesis is that exposure to PFCs may be associated with a higher risk of developing CVD.

See also Invited Commentary

Several lines of recent evidence suggest that an association between PFOA exposure and CVD may be biologically plausible. In epidemiological studies in humans, PFOA exposure has been linked to higher cholesterol levels,[12-16] which represent a strong, independent risk factor for CVD development.[17] Higher PFOA levels

Author Affiliations:
Department of Epidemiology, West Virginia University School of Public Health, Morgantown.

were shown to be related to insulin resistance and metabolic syndrome in a recent epidemiological study in adolescents and adults.[18] Insulin resistance and components of the metabolic syndrome have previously been shown to be associated with CVD development in epidemiological studies.[19] Finally, we have recently shown that higher PFOA levels are associated with serum uric acid levels,[20] a marker shown to be associated with an increased risk of developing CVD in epidemiological studies.[21] Despite these leads, to our knowledge, no previous study has examined the putative association between PFOA and CVD. We therefore examined the independent association between serum levels of PFOA and the presence of CVD and peripheral arterial disease (PAD), a marker of atherosclerosis, in a contemporary, nationally representative sample of US adults.

METHODS

The present study is based on merged data from the 1999-2000 and 2003-2004 National Health and Nutrition Examination Survey (NHANES). A detailed description of the NHANES study design and methods are available elsewhere.[22] In brief, the NHANES population included a stratified, multistage probability sample representative of the civilian noninstitutionalized US population. Selection was based on counties, blocks, households, and individuals within households and included the oversampling of low-income persons, persons 60 years or older, and African American and Mexican American persons to provide stable estimates of these groups. The survey included biomonitoring of PFC levels by the National Center for Environmental Health in a random one-third subsample of participants.

The present study sample consisted of 1327 NHANES participants 40 years or older who had measurements of PFOA levels and ankle-brachial index blood pressure (ABI) available. We excluded subjects with missing data (n = 111) on covariates included in the multivariable model, such as educational level, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), or cholesterol levels. The final sample consisted of 1216 participants (51.2% women).

MAIN OUTCOMES: CVD AND PAD

Participants were asked, "Has a doctor or other health professional ever told you that you have.... " in separate questions for coronary heart disease and stroke. The study defined CVD as physician-diagnosed coronary heart disease, heart attack, or stroke.[23]

We defined PAD in the present study using ABI. Details of methods used to measure ABI in NHANES have been described previously.[24] In brief, supine systolic blood pressure was measured with blood pressure cuffs on the right arm compressing the brachial artery and the 2 posterior tibial arteries. For subjects aged 40 to 59 years, 2 measurements were taken at each site and averaged per site, whereas for participants 60 years or older, one measurement was taken at each site. We calculated ABI as the ratio of the average ankle systolic blood pressure to the average arm systolic blood pressure. Participants with an ABI of at least 1.5 may have severe arterial rigidity and were therefore excluded from all analyses (n = 4). For the present study, PAD was defined as an ABI of less than 0.9, consistent with current guidelines[25] and national reports[24] using NHANES data.

EXPOSURE MEASUREMENTS

Age, sex, race/ethnicity, smoking status, alcohol intake, level of education, and medication use were assessed using a questionnaire. Rigorous procedures with quality control checks were used in blood collection, and details of these procedures are provided in the NHANES Laboratory/Medical Technologists Procedures Manual.[26] Levels of PFOA were measured in serum by the National Center for Environmental Health using automated solid-phase extraction coupled to isotope-dilution high-performance liquid chromatography–tandem mass spectrometry.[4] Perfluorooctanoic acid was detected in more than 98% of the study population. Values less than the limit of detection were reported by NHANES as the limit of detection divided by the square root of 2. The limit of detection for PFOA was 0.1 ng/mL, and the interassay coefficient of variation was 11%.[4]

Serum total cholesterol levels were measured enzymatically. Serum glucose levels were measured using the modified hexokinase method. Diabetes mellitus was defined based on the guidelines of the American Diabetes Association.[27] Seated systolic and diastolic blood pressures were measured using a mercury sphygmomanometer, and hypertension was defined according to the Seventh Joint National Committee recommendations.[28]

STATISTICAL ANALYSIS

We were interested in studying the association between increasing PFOA exposure and the presence of vascular disease. We initially performed separate analyses for the presence of CVD, PAD, and CVD or PAD as our 3 outcomes. Because results were similar, we are presenting herein the findings for the combined outcome. We categorized serum PFOA levels into quartiles based on sex because sex differences in PFOA levels have been well documented.[24,29-31] We used multivariable logistic regression models to calculate the odds ratio (OR [95% CI]) for the presence of CVD or PAD for each higher PFOA level by taking the lowest category as the reference level. We adjusted for the following variables in the multivariable model: age (in years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, or >high school), smoking status (never, former, or current), alcohol intake (none, moderate, or heavy), BMI, diabetes mellitus (absent or present), hypertension (absent or present), and serum total cholesterol level (in milligrams per deciliter). Trends in the OR of CVD or PAD across increasing serum PFOA levels were determined by modeling increasing PFOA categories as an ordinal variable. We examined the consistency of the association between serum PFOA and the presence of CVD or PAD by performing stratified analysis by sex, BMI, and smoking status. Sample weights that account for the unequal probabilities of selection, oversampling, and nonresponse and complex survey design were incorporated as recommended[22] in all analyses using commercially available software (SUDAAN, version 8.0 [Research Triangle Institute] and SAS, version 9.2 [SAS Institute, Inc]). We calculated SEs using the Taylor series linearization method.

RESULTS

Table 1 presents the baseline characteristics of the study population. Subjects with higher PFOA levels were more likely to be younger, non-Hispanic white, and heavy drinkers; were more likely to have education beyond high school, hypertension, and higher total cholesterol levels; and were less likely to be non-Hispanic black or Mexican American. Compared with subjects who were included in the final study sample, those who were excluded owing to missing covariate data were significantly younger but were similar with respect to other demographic and lifestyle characteristics listed in Table 1 (data not presented).

Table 1. Characteristics of the Study Population by Categories of PFOA Level[a]

Characteristic	PFOA Level, Quartile[b]				P Value
	1	2	3	4	
No. at risk	303	301	300	312	
Age, mean (SE), y	57.2 (0.8)	56.1 (1.1)	57.0 (0.6)	53.9 (0.5)	<.001
Women	52.8	55.2	48.6	49.0	.40
Race/ethnicity					
Non-Hispanic white	71.6	79.1	81.6	83.7	<.001
Non-Hispanic black	12.3	8.8	7.9	6.8	.009
Mexican American	9.1	5.9	4.5	2.4	<.001
Other	6.9	6.2	6.0	7.1	.92
Educational level					
<High school	22.8	18.1	19.0	11.8	.11
High school	34.1	30.6	29.9	26.3	.16
>High school	43.1	51.3	51.1	61.9	.006
Smoking status					
Never	45.3	44.0	41.4	46.0	.94
Former	34.3	32.5	38.3	34.1	.79
Current	20.5	23.5	20.3	19.9	.70
Alcohol intake					
None	43.3	39.7	40.0	29.8	.06
Moderate	43.1	43.7	34.7	48.5	.60
Heavy	13.6	16.6	25.4	21.7	.006
BMI, mean (SE)	28.8 (0.6)	28.2 (0.4)	29.0 (0.4)	28.3 (0.4)	.07
Diabetes mellitus	18.8	13.7	12.9	12.7	.17
Hypertension	46.3	43.1	49.0	52.7	.06
Total cholesterol level, mean (SE), mg/dL	206.4 (4.4)	211.8 (3.5)	212.3 (2.7)	217.7 (2.4)	.11

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PFOA, perfluorooctanoic acid.
SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
[a] Unless otherwise indicated, data are expressed as row percentages of subjects. Percentages have been rounded and might not total 100.
[b] The following PFOA levels were used for quartiles in women: less than 2.9 ng/mL (quartile 1), 2.9 to 3.9 ng/mL (quartile 2), 4.0 to 5.6 ng/mL (quartile 3), and greater than 5.6 ng/mL (quartile 4); in men: less than 3.0 ng/mL (quartile 1), 3.0 to 4.3 ng/mL (quartile 2), 4.4 to 6.1 ng/mL (quartile 3), and greater than 6.1 ng/mL (quartile 4).

Table 2. Association Between Serum PFOA Level and the Presence of CVD or PAD

PFOA Quartile[a]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]		
		Presence of CVD	Presence of PAD	Presence of CVD or PAD
1	303	1 [Reference]	1 [Reference]	1 [Reference]
2	301	1.58 (0.80-3.12)	0.75 (0.37-1.52)	1.41 (0.81-2.45)
3	300	1.77 (1.04-3.02)	1.18 (0.47-2.96)	1.72 (1.13-2.64)
4	312	2.01 (1.12-3.60)	1.78 (1.03-3.08)	2.28 (1.40-3.71)
P value for trend		.01	.04	<.001

Abbreviations: CVD, cardiovascular disease; OR, odds ratio; PAD, peripheral arterial disease; PFOA, perfluorooctanoic acid.
[a] For quartiles of plasma PFOA levels in women and men, see Table 1.
[b] Adjusted for age (in years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, or >high school), smoking status (never, former, or current), alcohol intake (none, moderate, or heavy), body mass index, hypertension (absent or present), diabetes mellitus (absent or present), and serum total cholesterol level (in milligrams per deciliter).

Table 2 presents the results of analyses examining the association between increasing serum levels of PFOA and the presence of CVD or PAD. Overall, we found that increasing levels of PFOA were significantly associated with CVD and PAD in the multivariable-adjusted model. Models evaluating trend in this association were also statistically significant.

In separate analyses, we also examined the association between increasing levels of PFOA and components of CVD, including coronary heart disease and stroke (see eTable 1; http://www.archinternmed.com). Compared with subjects in quartile 1 of PFOA levels, the multivariable-adjusted OR (95% CI) in quartile 4 was 2.24 (1.02-4.94) for the presence of coronary heart disease and 4.26 (1.84-9.89) for the presence of stroke.

Tables 3, **4**, and **5** present the association between increasing serum levels of PFOA and the presence of CVD or PAD within subgroups of sex, smoking status, and BMI, respectively. Overall, consistent with the findings for the whole cohort, we found that higher PFOA levels were associated with the presence of CVD or PAD within these stratified subgroups also ($P > .10$ for interaction in all subgroup analyses). However, some of the ORs failed to reach conventional levels of statistical significance owing to reduction in sample size and therefore inadequate statistical power within categories.

Table 3. Association Between Serum PFOA Level and the Presence of CVD or PAD by Sex

	Men		Women	
PFOA Quartile[a]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]
1	151	1 [Reference]	152	1 [Reference]
2	159	1.59 (0.56-4.47)	142	1.36 (0.78-2.37)
3	158	1.75 (1.04-2.96)	142	1.88 (0.98-3.63)
4	155	1.83 (1.02-3.28)	157	2.99 (1.53-5.81)
P value for trend		.04		.004

Abbreviations: CVD, cardiovascular disease; OR, odds ratio; PAD, peripheral arterial disease; PFOA, perfluorooctanoic acid.
[a] For quartiles of plasma PFOA levels in women and men, see Table 1.
[b] Adjusted for age (in years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, or >high school), smoking status (never, former, or current), alcohol intake (none, moderate, or heavy), body mass index, hypertension (absent or present), diabetes mellitus (absent or present), and serum total cholesterol level (in milligrams per deciliter).

Table 4. Association Between Serum PFOA Level and the Presence of CVD or PAD by Smoking Status

	Never or Former Smoker		Current Smoker	
PFOA Quartile[a]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]
1	258	1 [Reference]	45	1 [Reference]
2	240	1.36 (0.74-2.48)	61	2.26 (0.78-6.55)
3	242	1.98 (1.16-3.37)	58	1.27 (0.35-4.63)
4	249	2.40 (1.37-4.21)	63	2.15 (0.35-13.22)
P value for trend		.001		.59

Abbreviations: CVD, cardiovascular disease; OR, odds ratio; PAD, peripheral arterial disease; PFOA, perfluorooctanoic acid.
[a] For quartiles of plasma PFOA levels in women and men, see Table 1.
[b] Adjusted for age (in years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, or >high school), alcohol intake (none, moderate, or heavy), body mass index, hypertension (absent or present), diabetes mellitus (absent or present), and serum total cholesterol level (in milligrams per deciliter).

Table 5. Association Between Serum PFOA Level and the Presence of CVD or PAD by BMI Categories

	BMI <30		BMI ≥30	
PFOA Quartile[a]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]	Unweighted Sample Size	Multivariable-Adjusted OR (95% CI)[b]
1	189	1 [Reference]	114	1 [Reference]
2	197	1.58 (0.75-3.30)	104	1.25 (0.56-2.77)
3	198	1.62 (0.79-3.32)	102	1.87 (0.73-4.79)
4	203	1.82 (1.01-3.54)	109	2.98 (1.40-6.37)
P value for trend		.06		.002

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; OR, odds ratio; PAD, peripheral arterial disease; PFOA, perfluorooctanoic acid.
[a] For quartiles of plasma PFOA levels in women and men, see Table 1.
[b] Adjusted for age (in years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, or >high school), smoking status (never, former, or current), alcohol intake (none, moderate, or heavy), hypertension (absent or present), diabetes mellitus (absent or present), and serum total cholesterol level (in milligrams per deciliter).

Finally, in a supplementary analysis, we examined the association between increasing quartiles of PFOA level and the presence of CVD or PAD with additional adjustments for serum high-sensitivity C-reactive protein and serum uric acid levels (see eTable 2) in the multivariable-adjusted model; the overall results were essentially the same, although the ORs were slightly attenuated.

COMMENT

In a nationally representative sample of US adults, we found that higher PFOA levels were positively associated with the presence of CVD and PAD. This association appeared to be independent of traditional confounders such as age, sex, race/ethnicity, smoking status, heavy alcohol intake, BMI, diabetes mellitus, hypertension, and serum cholesterol level. In subgroup analyses, we found that higher PFOA levels were positively associated with CVD or PAD in men as well as women, nonobese as well as obese subjects, and nonsmokers as well as current smokers. Our results contribute to the emerging data[12,13,20] on health effects of PFCs, suggesting for the first time that PFOA exposure is potentially related to CVD and PAD. However, owing to the cross-sectional nature of the

present study, we cannot conclude that the association is causal.

Perfluorooctanoic acid belongs to a family of synthetic, highly stable, perfluorinated compounds.[1-3] The chemical is widely used in industrial and consumer products, including stain- and water-resistant coatings for carpets and fabrics, fast-food contact materials, food packaging, fire-resistant foams, paints, and hydraulic fluids.[1,3] Additional sources of PFOA exposure to humans are through drinking water, outdoor and indoor air, dust, and food packaging.[3] Recently, Schecter et al[32] showed that commonly consumed meat, fish, and plant products in US supermarkets are contaminated by PFOA. General population studies have shown that in addition to the near-ubiquitous presence of PFOA in blood of Americans, the chemical may also be present in breast milk, seminal fluid, and umbilical cord blood.[2] Perfluorooctanoic acid binds to serum proteins and has a relatively long half-life.[5] The carbon-fluoride bonds that make PFOA useful as a surfactant are highly stable, which also makes the chemical resistant to biogradation; consequently, recent reports indicate the widespread persistence of PFOA in the environment and in wildlife and human populations globally.[1,2] Owing to the pervasive presence of PFOA, its public health effects are a concern.

Several lines of recent evidence suggest that an association between PFOA and the presence of CVD and PAD may be plausible. First, in vitro studies suggest that exposure to PFOA is associated with higher oxidative stress[33-35] and endothelial dysfunction.[36,37] Higher oxidative stress and endothelial dysfunction in turn are considered to be mechanisms involved in atherosclerosis and CVD development.[38-40] Second, exposure to PFOA has been associated with marked accumulation of triglycerides and lipids in the liver of rats[41,42] and induction of peroxisomal α- and β-oxidation.[43] Studies in animal models suggest that PFOA adversely affects the peroxisome proliferator-activated receptor α and related inflammatory pathways,[44] thereby potentially contributing to the development of CVD.[45] Third, in humans, serum PFOA levels have been found to be positively associated with serum cholesterol levels in several occupational studies[14-16] and 1 community-based study.[13] Recently, in the C8 Health Project, a large population-based study of community residents from Ohio and West Virginia who were exposed to PFOA through their drinking water, the authors showed that serum levels of PFOA are independently associated with high serum total and low-density lipoprotein cholesterol levels in adults[12] and in children and adolescents.[46] Also, Olsen and Zobel[16] reported a modest negative association between PFOA and serum high-density lipoprotein cholesterol levels and a positive association between PFOA and serum triglyceride levels. In this regard, higher serum total and low-density lipoprotein cholesterol and triglyceride levels and low high-density lipoprotein cholesterol levels are known to be independent risk factors for CVD.[17] Fourth, serum PFOA levels have been reported to be positively associated with insulin resistance[13] and components of the metabolic syndrome,[18] factors that have been shown to be associated with CVD development.[19] Sixth, PFOA exposure has been found to be significantly associated with elevated serum uric acid levels in a previous cross-sectional study of 1000 workers at a PFOA production plant.[14] Using data from the C8 Health Project, we also recently reported that PFOA levels were independently associated with high serum uric acid levels.[20] Several studies have in turn shown that higher serum uric acid levels are related to increased risk of CVD and CVD mortality.[21] Seventh, again using data from the C8 Health Project, we recently reported an inverse association between serum PFOA and estradiol levels in women.[47] Decreased serum estrogen levels have been reported to be associated with higher risk of CVD.[48] Eighth, recent studies have reported a positive association between serum levels of PFOA and γ-glutamyltransferase,[49] another biomarker related to liver function and oxidative stress that has been shown to independently predict CVD[50] and PAD.[51] Ninth, recent reports from NHANES suggest that PFOA levels are related to thyroid dysfunction,[52] a factor that has been reported to be associated with CVD.[53]

To date, only 3 studies have been conducted on the putative association between higher PFOA levels and CVD, and their results have not been consistent.[52,54,55] In a population of 566 white community residents exposed to PFOA via drinking water, Anderson-Mahoney et al[54] reported a statistically significant higher age-adjusted (via indirect standardization) prevalence of self-reported angina, myocardial infarction, and stroke compared with controls selected from NHANES data. Similarly, in an occupational cohort of employees from a PFOA manufacturing facility, Lundin et al[55] reported a positive, albeit statistically nonsignificant, trend of stroke mortality across nonexposed, probably exposed, and definitely exposed job categories using indirect standardization. However, both studies performed only indirect age standardization and did not account for other important confounders, such as smoking status, BMI, diabetes mellitus, hypertension, or serum cholesterol levels. In contrast, Melzer et al[52] examined data from the NHANES study and reported no significant association between PFOA levels and self-reported CVD. The latter study, however, did not adjust for important confounding factors, such as diabetes, hypertension, or serum cholesterol levels, and the authors examined only self-reported CVD, which is prone to misclassification, as opposed to objectively measured outcome measures.

In this context, our results from a contemporary, nationally representative sample of US adults are relevant. We found an independent association between serum PFOA levels and the presence of self-reported CVD and objectively measured PAD. The observed associations were found to be independent of confounders, such as age, sex, smoking status, BMI, diabetes mellitus, hypertension, and serum cholesterol, serum uric acid, and serum high-sensitivity C-reactive protein levels, and consistently present within the subgroups of sex, smoking status, and BMI, suggesting that these findings are not likely to be due to chance.

The public health importance of our findings is that serum PFOA levels appear to be positively related to these common CVD outcomes even at relatively low, "background" exposure levels in the US general population. Because all PFOA is manmade, this excess risk may be

removed or substantially mitigated through regulation or by emerging pharmacological means that need to be further studied (eg, using bile acid sequestrants[56]). Therefore, if our findings are replicated in future prospective studies, the population-attributable risk of PFOA exposure on CVD risk could potentially be high.

The main strengths of our study include its population-based nature, inclusion of a representative multiethnic sample, adequate sample size, and the availability of detailed data on confounders for multivariable adjustment. Furthermore, all data were collected following rigorous methods, including a study protocol with standardized quality control checks. The main limitation of our study is the cross-sectional nature of NHANES. Therefore, similar to previous studies that examined the association between other environmental exposures and disease states using the NHANES data (eg, bisphenol A levels and CVD[23]), the temporal nature of the association between PFOA and CVD cannot be concluded from the present study. Second, our study does not have the data to estimate the sources of exposure to PFOA. Future studies should examine sources of PFOA in addition to serum levels for identifying preventive measures to limit exposure. Third, the pharmacokinetics of PFOA in humans have not yet been completely elucidated; studies available to date have reported a wide range of values for serum half-life. Accurate identification of half-life is important to interpret the observed association of serum PFOA levels to CVD in humans. Fourth, we are examining PFOA levels measured in the serum at just one point. This point may not provide an accurate estimate of the average or the cumulative effect of PFOA exposure across several years; epidemiological studies measuring PFOA levels at multiple points are needed for this purpose. Fifth, owing to the cross-sectional nature of our study, we may have missed subjects who died of CVD, which is our main outcome. Finally, because CVD was ascertained by self-report, some recollection bias may exist. These last two study limitations may have resulted in outcome misclassification that in turn may have biased our results toward or away from the null.

In summary, in a representative cross-sectional sample of the US population, we found that higher PFOA levels are positively associated with self-reported CVD and objectively measured PAD. Our findings, however, should be interpreted with caution because of the possibility of residual confounding and reverse causality. Future prospective studies are needed to confirm or refute our findings.

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Correspondence: Anoop Shankar, MD, PhD, Department of Epidemiology, West Virginia University School of Public Health, 1 Medical Center Dr, PO Box 9190, Morgantown, WV 26506 (ashankar@hsc.wvu.edu).
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Supplementary Online Content

Shankar A, Xiao J, Ducatman A. Perfuorooctanoic acid and cardiovascular disease in US adults. *Arch Intern Med.* 2012. doi:10.1001/archinternmed.2012.3393.

eTable 1. Association between serum PFOA level and the presence of CHD or stroke

eTable 2. Association between serum PFOA level and the presence of CVD or PAD, additionally adding serum high-sensitivity CRP and uric acid levels into the multivariable model

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Association between serum PFOA level and presence of CHD or stroke

	Presence of CHD	Presence of stroke
Quartile	Multivariable-adjusted OR (95% CI)‡	Multivariable-adjusted OR (95% CI)‡
PFOA*		
Quartile 1	1.00 (Reference)	1.00 (Reference)
Quartile 2	0.90 (0.37-2.23)	4.39 (1.44-13.37)
Quartile 3	1.90 (0.89-4.08)	3.94 (1.48-10.50)
Quartile 4	2.24 (1.02-4.94)	4.26 (1.84-9.89)
P Value for trend	.007	.02

* We used the following plasma PFOA level quartiles in women: quartile 1 (<2.9 ng/mL), quartile 2 (2.9-3.9 ng/mL), quartile 3 (4.0-5.6 ng/mL), and quartile 4 (>5.6 ng/mL); in men: quartile 1 (<3.0 ng/mL), quartile 2 (3.0-4.3 ng/mL), quartile 3 (4.4-6.1 ng/mL), and quartile 4 (>6.1 ng/mL)

‡Adjusted for age (years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, >high school), alcohol intake (none, moderate, or heavy), body mass index, hypertension (absent or present), diabetes mellitus (absent or present), and serum total cholesterol level (in mg/dL).

Abbreviations: CHD, coronary heart disease; OR, odds ratio; PFOA, perfluorooctanoic acid.

eTable2. Association between serum PFOA level and the presence of CVD or PAD, additionally adding serum high-sensitivity CRP and uric acid levels into the multivariable model

	Presence of CVD	Presence of PAD	Presence of CVD or PAD
Quartile	Multivariable-adjusted OR (95% CI)‡	Multivariable-adjusted OR (95% CI)‡	Multivariable-adjusted OR (95% CI)‡
PFOA*			
Quartile 1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.55 (0.79-3.04)	0.74 (0.36-1.50)	1.40 (0.81-2.41)
Quartile 3	1.71 (1.01-2.90)	1.15 (0.47-2.85)	1.69 (1.12-2.54)
Quartile 4	1.93 (1.08-3.45)	1.75 (1.00-3.03)	2.22 (1.38-3.59)
P Value for trend	.02	.046	<.001

* We used the following plasma PFOA level quartiles in women: quartile 1 (<2.9 ng/mL), quartile 2 (2.9-3.9 ng/mL), quartile 3 (4.0-5.6 ng/mL), and quartile 4 (>5.6 ng/mL); in men: quartile 1 (<3.0 ng/mL), quartile 2 (3.0-4.3 ng/mL), quartile 3 (4.4-6.1 ng/mL), and quartile 4 (>6.1 ng/mL)

‡Adjusted for age (years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (<high school, high school, >high school), smoking status (never, former, or current), alcohol intake (none, moderate, or heavy), body mass index, hypertension (absent or present), diabetes mellitus (absent or present), serum total cholesterol level (in mg/dL), serum high-sensitivity CRP level (in mg/dL), and serum uric acid level (in mg/dL).

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; OR, odds ratio; PAD, peripheral arterial disease; PFOA, perfluorooctanoic acid.