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.

viously been shown to be associated with CVD development in epidemiological studies.

Finally, we have recently shown that higher PFOA levels are associated with serum uric acid levels, a marker shown to be associated with an increased risk of developing CVD in epidemiological studies. 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. 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.

We defined PAD in the present study using ABI. Details of methods used to measure ABI in NHANES have been described previously. 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 and national reports using NHANES data. The weighted prevalences of the outcomes used in the present analyses were CVD, 13.0%; PAD, 4.3%; and CVD or PAD, 16.6%.

### 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. 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. 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%.

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.

Seated systolic and diastolic blood pressures were measured using a mercury sphygmomanometer, and hypertension was defined according to the Seventh Joint National Committee recommendations.

### 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. 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), education (≤ 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 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.

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 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://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.
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.

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, 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 current smokers. Our results contribute to the emerging data 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

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

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

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

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

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

<table>
<thead>
<tr>
<th>PFOA Quartile</th>
<th>BMI &lt; 30</th>
<th></th>
<th>Multivariable-Adjusted OR (95% CI)</th>
<th>BMI ≥ 30</th>
<th></th>
<th>Multivariable-Adjusted OR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Unweighted Sample Size</td>
<td></td>
<td></td>
<td>Unweighted Sample Size</td>
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<tr>
<td>1</td>
<td>189</td>
<td>1</td>
<td>[Reference]</td>
<td>114</td>
<td>1</td>
<td>[Reference]</td>
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<tr>
<td>2</td>
<td>197</td>
<td>1.58 (0.75-3.30)</td>
<td></td>
<td>104</td>
<td>1.25 (0.56-2.77)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>198</td>
<td>1.62 (0.79-3.32)</td>
<td></td>
<td>102</td>
<td>1.87 (0.73-4.79)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>203</td>
<td>1.82 (1.01-3.54)</td>
<td></td>
<td>109</td>
<td>2.98 (1.40-6.37)</td>
<td></td>
</tr>
<tr>
<td>P value for trend</td>
<td>.06</td>
<td></td>
<td></td>
<td>.002</td>
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</table>
present study, we cannot conclude that the association is causal.

Perfluorooctanoic acid belongs to a family of synthetic, highly stable, perfluorinated compounds. 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. Additional sources of PFOA exposure to humans are through drinking water, outdoor and indoor air, dust, and food packaging. Recently, Schecter et al 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. Perfluorooctanoic acid binds to serum proteins and has a relatively long half-life. 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. 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 and endothelial dysfunction; consequently, recent reports indicate the widespread persistence of PFOA in the environment and in wildlife and human populations globally. Owing to the pervasive presence of PFOA, its public health effects are a concern.

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removed or substantially mitigated through regulation or by emerging pharmacological means that need to be further studied (eg, using bile acid sequestrants). 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), 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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Author Contributions: Study concept and design: Shankar and Ducatman. Acquisition of data: Shankar. Analysis and interpretation of data: Shankar, Xiao, and Ducatman. Drafting of the manuscript: Shankar. Critical revision of the manuscript for important intellectual content: Shankar, Xiao, and Ducatman. Statistical analysis: Shankar and Xiao. Obtained funding: Shankar. Administrative, technical, and material support: Shankar and Ducatman.

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Perfluorooctanoic Acid Exposure and Cardiovascular Disease

Potential Role and Preventive Measures

Cardiovascular disease (CVD) remains the most common cause of morbidity and mortality in the United States. In 2008, the overall rate of deaths attributable to CVD was 244.8 per 100,000,1 and currently more than 2200 Americans die of CVD each day, an average of 1 death every 39 seconds.1 Although the large case-control study Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction in 52 Countries (INTERHEART) suggested that lipid levels; smoking; hypertension; diabetes mellitus; abdominal obesity; psychosocial factors; consumption of fruits, vegetables, and alcohol; and degree of physical activity account for most