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Positive Association Between Perfluoroalkyl Chemicals and Hyperuricemia in Children

Sarah Dee Geiger*, Jie Xiao, and Anoop Shankar

* Correspondence to Dr. Sarah Dee Geiger, University of Wisconsin Population Health Institute, Room 575 WARF, 614 Walnut Street, Madison, WI 53726 (e-mail: sarahdeemurphy@gmail.com).

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Hyperuricemia in children is associated with increased risk of high blood pressure, metabolic syndrome, and future cardiovascular disease. Serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) levels have been shown to be positively associated with hyperuricemia in adults, but the association in children remains unexplored. We therefore examined the association between serum PFOA and PFOS levels and hyperuricemia in a representative sample of US children. A cross-sectional study was performed on 1,772 participants ≤18 years of age from the National Health and Nutrition Examination Survey 1999–2000 and 2003–2008. The main outcome of interest was hyperuricemia, defined as serum uric acid levels ≥6 mg/dL. We found that serum levels of PFOA and PFOS were positively associated with hyperuricemia, independent of age, sex, race/ethnicity, body mass index, annual household income, physical activity, serum total cholesterol, and serum cotinine levels. Compared with subjects in quartile 1 (referent), subjects in quartile 4 had multivariable-adjusted odds ratios for hyperuricemia of 1.62 (95% confidence interval: 1.10, 2.37) for PFOA and 1.65 (95% confidence interval: 1.10, 2.49) for PFOS. Our findings indicate that serum perfluoroalkyl chemical levels are significantly associated with hyperuricemia in children even at the lower "background" exposure levels of the US general population.

hyperuricemia; NHANES; pediatrics; perfluoroalkyl chemicals; perfluorooctane sulfonate; perfluorooctanoic acid; PFC; uric acid

Abbreviations: CI, confidence interval; LLOD, lower limit of detection; NHANES, National Health and Nutrition Examination Survey; PFC, perfluoroalkyl chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are 2 of the most studied types of perfluoroalkyl chemicals (PFCs). These chemicals persist in the environment, bioaccumulate, biomagnify along food chains, and have been shown to cause developmental, endocrine, and other adverse health outcomes in laboratory animals (1, 2). Reports from national biomonitoring surveys suggest that detectable levels of PFCs are present in the blood of more than 98% of the US population (3). Known routes of exposure include inhalation, ingestion, and absorption through the skin (4–9). Potential exposure sources are surfactants, lubricants, polishes, paper and textile coatings, food packaging, and fire-retarding foams, as well as household dust and vegetables and meat products from supermarkets (2, 3, 10, 11). Children tend to experience higher uptake of PFCs than adults, but the relative contribution of each source is unknown (12).

Uric acid is a byproduct of purine metabolism with both oxidant and antioxidant properties (13, 14). Elevated serum uric acid levels have an underlying role in gout (15), and studies have shown that moderate elevations in uric acid are also associated with dyslipidemia (16), increased systemic inflammation (17), insulin resistance (18), diabetes mellitus (19), hypertension (20), chronic kidney disease (21), and cardiovascular disease (22). Similarly, studies focused on children have reported associations between elevations in

serum uric acid levels and increased risk of hypertension (23), childhood metabolic syndrome (24–28), and several other cardiometabolic risk factors (23).

Existing studies in populations that are highly exposed to PFCs have demonstrated a positive relationship between exposure to PFCs and elevated serum uric acid in adults (29–32). These studies include occupational cohorts of employees from PFC-handling chemical plants (30, 31) as well as a community-based study of residents from the Ohio River valley who were highly exposed to PFOA in drinking water after contamination of their drinking water source from a nearby chemical plant (32).

Recently, in a population-based study, Seals et al. (33) demonstrated that PFOA has a concentration-dependent half-life of 2.9 years at higher serum levels and 8.5 years at lower levels, suggesting that, at lower serum levels, PFCs persist in the body for a longer period of time. Given the fact that PFCs are present in the blood of the majority of Americans at low levels (3), in addition to studying population groups with high PFC exposure, it is also important to study the PFC–uric acid association at lower "background" exposure levels typically seen in US general population samples.

Furthermore, an important gap in current literature is the fact that the association between PFCs and serum uric acid has not, to our knowledge, been explored in children. Given the role of high serum uric acid levels in childhood metabolic syndrome and other cardiometabolic risk factors (23, 25–29) as well as the emerging consensus that the development of cardiovascular disease in adulthood is preceded by metabolic changes occurring in childhood (28, 34, 35), it is important to identify novel risk factors, including environmental factors, associated with hyperuricemia in children. Another advantage of studying associations in children is that, from an epidemiologic point of view, when compared with adults, children generally may have limited cumulative exposure to lifestyle/behavioral risk factors for chronic diseases such as smoking and alcohol intake, and therefore the potential for confounding by these factors tends to be limited. In this context, we sought to examine the association between PFCs and serum uric acid levels in children using National Health and Nutrition Examination Survey (NHANES) data.

MATERIALS AND METHODS

Study population

This study uses 8 years of merged data from NHANES, 1999–2000, 2003–2004, 2005–2006, and 2007–2008. PFC data were not available for NHANES 2001–2002. Data collection methods for NHANES have been published and are available online (36). NHANES included a stratified multistage probability sample representative of the civilian noninstitutionalized population in the United States. Selection was based on counties, census blocks, households, and individuals within households and included the oversampling of non-Hispanic blacks and Mexican Americans in order to provide stable estimates of these groups. Subjects were required to sign a consent form before their participation, and approval was obtained from the Human Subjects Committee in the US Department of Health and Human Services. The survey also included biomonitoring for select environmental chemicals, including perfluoroalkyl chemicals, in a random one-third subsample of participants by the National Center for Environmental Health.

The central variables for this analysis are laboratory measurements of PFOA, PFOS, and uric acid. Our study sample consisted of children 18 years of age or younger who took part in both the interview and examination components; because NHANES does not sample PFC levels for children under age 12, the age range for this study is children 12–18 years ($n = 1{,}919$). We then excluded those with missing values for important covariates used in the multivariable model, namely, age, sex, race/ethnicity, annual household income, physical activity, serum total cholesterol, and serum cotinine ($n = 147$). The final sample size of children available for this analysis was 1,772.

Main outcome of interest: uric acid

The main outcome of interest was the serum uric acid level or the presence of hyperuricemia. Uric acid was measured by using the Beckman Synchron LX20 system (Beckman Coulter, Brea, California). Details of laboratory measurement are available online (37). Summarily, oxidization of uric acid by uricase produces allantoin and hydrogen peroxide. Hydrogen peroxide reacts with 4-aminoantipyrine and 3,5-dichloro-2-hydroxybenzene sulfonate in a reaction catalyzed by peroxidase, which yields a colored product. The Beckman Synchron LX20 system monitors the change in absorbance at 520 nm at a fixed time interval. Change in absorbance is directly proportional to the concentration of uric acid in the sample. The Coulston Foundation at Alamogordo, New Mexico, performed testing in 1999–2000, and Collaborative Laboratory Services at Ottumwa, Iowa, began testing in 2003–2004. Consistent with definitions in previous publications in the field, hyperuricemia in children was defined as serum uric acid levels ≥6 mg/dL (38, 39). In addition, we conducted analyses using other cutoff values, including >5.5 mg/dL (26), ≥7.7 mg/dL for males and ≥5.7 mg/dL for females (40), and ≥5.5 mg/dL for females and ≥7 mg/dL for females (41).

Exposure measurements

Gender, age, race/ethnicity, educational level, physical activity, and annual household income were assessed by a standardized interview. Using standard procedures, age- and sex-specific body mass index z scores were obtained for each child based on how his/her body mass index value compared with the referent population of the US National Center for Health Statistics (42). A SAS macro (SAS Institute, Inc., Cary, North Carolina) provided by the Centers for Disease Control and Prevention was used to derive z scores based on each child's exact age in 1-month intervals. As recommended (42), the underweight category was defined as a body mass index z score below the 5th percentile of the referent population, healthy weight as a body mass index z score between the 5th and 84th percentiles, being at risk of overweight as a body mass index z score between the 85th

and 94th percentiles, and obesity as a body mass index z score greater than or equal to the 95th percentile. NHANES participants also provided blood samples for various laboratory measurements. Details of blood collection and analysis are provided in the NHANES laboratory/medical technologists procedures manual (43). Briefly, serum total cholesterol was measured enzymatically. Perfluoroalkyl chemicals were measured in serum by the National Center for Environmental Health by using automated solid-phase extraction coupled to isotope dilution high-performance liquid chromatography–tandem mass spectrometry. Our study focused on 2 types of PFCs—PFOA and PFOS. Both were detected in the serum of over 98% of participants; values below the lower limit of detection (LLOD) were reported by NHANES as the limit of detection divided by the square root of 2. The LLOD for PFOA was 0.1 ppb for all years (36). The LLOD for PFOS was 0.4 ppb in years 2003–2004 and 0.2 ppb in years 2005–2008 (36). Quality control checks were implemented throughout PFC measurement procedures to include repeat testing on 2% of all specimens and performing blind split samples collected on "dry run" sessions. Details are available in the NHANES laboratory/medical technologists procedures manual (43). The National Center for Environmental Health measured serum PFC levels using automated solid-phase extraction coupled to isotope dilution high-performance liquid chromatography–tandem mass spectrometry. Detailed laboratory methods are available online (43).

Statistical analysis

Serum PFOA and PFOS were analyzed as continuous as well as categorical variables. For analysis as a continuous variable, PFC values were log-transformed (base e) to correct skewed distributions. We also categorized PFCs into quartiles of increasing exposure. We ran linear regression models with serum PFC quartiles as the independent variable to examine the mean change in serum uric acid with increasing categories of PFC, using quartile 1 as the referent. We ran 2 nested models: 1) unadjusted and 2) multivariable-adjusted, controlling for age (years), sex (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), body mass index (underweight, healthy weight, overweight, obese), annual household income categories (≤$4,999, $5,000–$9,999, $10,000–$14,999, $15,000–$19,999, $20,000–$24,999, $25,000–$34,999, $35,000–$44,999, $45,000–$54,999, $55,000–$64,999, $65,000–$74,999, ≥$75,000), moderate activity (absent, present), serum total cholesterol (mg/dL), and serum cotinine (ng/mL). We also ran multivariable logistic regression models to calculate the odds ratio and 95% confidence interval of hyperuricemia for each PFC quartile, with quartile 1 as the referent. Trends in the odds ratio of hyperuricemia across increasing serum PFC quartiles were determined by modeling the PFCs as ordinal variables. We applied sample weights that account for unequal probabilities of selection, oversampling, and nonresponse in NHANES for all analyses, as recommended by the National Center for Health Statistics (43). Analyses were conducted by using SAS, version 9.2, software (SAS Institute, Inc.). Standard errors were estimated by using the Taylor series linearization method.

Table 1. Characteristics of the Study Population, NHANES, 1999–2008

Study Population Characteristics ($n = 1,772$[a])	%	Mean (SE)
Age, years		15.0 (0.1)
Women	48.1	
Race/ethnicity		
Non-Hispanic white	62.5	
Non-Hispanic black	14.5	
Mexican American	11.5	
Other	11.6	
Annual household income		
Under $25,000	23.5	
$25,000–$54,999	27.9	
$55,000 and over	48.6	
No moderate activity	18.2	
Body mass index category		
Underweight	4.4	
Healthy weight	58.9	
Overweight	17.8	
Obese	18.9	
Total cholesterol, mg/dL		159.7 (1.0)
Serum cotinine, ng/mL		14.8 (1.6)
Uric acid, mg/dL		5.1 (0.04)
PFOA, ng/mL		4.3 (0.1)
PFOS, ng/mL		18.4 (0.5)

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SE, standard error.
[a] Unweighted sample size.

RESULTS

Table 1 presents characteristics of the study population ($n = 1,772$). The mean age was 15 years, and nearly half of the study population was female. Blacks comprised 14.5% of the study population, and Mexican Americans made up 11.5%. Over 48% of study participants had an annual household income of over $55,000. About 18% reported no moderate physical activity, and 36.7% of the children were overweight or obese.

Table 2 illustrates the association between increasing quartiles of serum PFOA and PFOS and the change in mean serum uric acid level (mg/dL) using linear regression models. We observed a positive, statistically significant association between increasing quartiles of PFOA and serum uric acid in both the unadjusted and multivariable-adjusted models ($P_{trend} \leq 0.0001$ for both models). For PFOS, a similar positive association was observed in the unadjusted model ($P_{trend} = 0.0147$), which was found to be

Table 2. Association Between Serum PFOA and PFOS Levels and Serum Uric Acid Levels, NHANES, 1999–2008

Plasma PFC Level	Sample Size	Unadjusted Mean Change in Serum Uric Acid, mg/dL	95% CI	Multivariable-adjusted Mean Change in Serum Uric Acid, mg/dL[a]	95% CI
PFOA[b]					
Quartile 1	437	0	Referent	0	Referent
Quartile 2	462	0.23	0.09, 0.38	0.02	−0.10, 0.14
Quartile 3	434	0.27	0.10, 0.44	0.03	−0.11, 0.17
Quartile 4	439	0.66	0.50, 0.82	0.30	0.17, 0.43
P_{trend}		<0.0001		0.0001	
Log-transformed PFOA		0.43	0.32, 0.53	0.20	0.11, 0.29
PFOS[c]					
Quartile 1	444	0	Referent	0	Referent
Quartile 2	437	0.08	−0.07, 0.23	0.03	−0.10, 0.16
Quartile 3	448	0.11	−0.03, 0.26	0.09	−0.04, 0.21
Quartile 4	443	0.22	0.05, 0.39	0.12	−0.01, 0.26
P_{trend}		0.0147		0.0575	
Log-transformed PFOS		0.14	0.05, 0.23	0.09	0.02, 0.17

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; PFC, perfluoroalkyl chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

[a] Adjusted for age (years), sex (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), body mass index, categories (underweight, healthy weight, overweight, obese), annual household income categories, moderate activity (absent, present), total cholesterol (mg/dL), and serum cotinine (ng/mL).

[b] Plasma PFOA quartiles: quartile 1 (<2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), and quartile 4 (>5.4 ppb).

[c] Plasma PFOS quartiles: quartile 1 (<10.7 ppb), quartile 2 (10.7–16.5 ppb), quartile 3 (16.6–25.5 ppb), and quartile 4 (>25.5 ppb).

attenuated after multivariable adjustment ($P_{trend} = 0.0575$). Log-transformed PFOA and PFOS also showed similar positive associations with serum uric acid.

Table 3 presents the association between increasing quartiles of serum PFOA and PFOS and hyperuricemia using logistic regression models. Because a standard definition for hyperuricemia in children has not been established, we chose serum uric acid levels ≥6 mg/dL (38, 39) on the basis of prior literature for the results in Table 3. Similar to results from the linear regression analysis, overall, we observed a positive, statistically significant association between increasing quartiles of PFOA and PFOS and hyperuricemia in all models. In the unadjusted model, a positive association with hyperuricemia was evident for both increasing quartiles of PFOA ($P_{trend} < 0.0001$) and PFOS ($P_{trend} = 0.003$). The positive association remained after multivariable adjustment for increasing quartiles of PFOA ($P_{trend} = 0.0071$) and PFOS ($P_{trend} = 0.0221$). In a series of supplementary analyses, we examined alternate cutoffs for hyperuricemia, including >5.5 mg/dL (26), ≥7.7 mg/dL for males and ≥5.7 mg/dL for females (40), and ≥5.5 mg/dL for females and ≥7 mg/dL for females (41); these analyses yielded similar results overall. In another supplementary analysis, we included smoking while pregnant and household smoking as covariates in the multivariable models (Appendix Table 1). In both linear and logistic regression analyses, results were consistent with analyses that did not control for these variables. Compared with that for subjects in quartile 1, the multivariable-adjusted odds ratio for hyperuricemia among children in quartile 4 was 1.61 (95% CI: 1.11, 2.35) for PFOA and 1.64 (95% CI: 1.09, 2.47) for PFOS (data not shown).

DISCUSSION

We found a positive association between exposure to PFOA and PFOS and elevated serum uric acid levels in a nationally representative sample of children. Furthermore, this association was found to be independent of age, sex, race/ethnicity, body mass index, annual household income, moderate activity, serum total cholesterol, and serum cotinine levels. Our results contribute to the extant literature by reporting the PFC–uric acid association for the first time in children.

Elevated serum uric acid levels have an underlying role in the pathophysiology of gout (15). Gout results from deposition of monosodium urate crystals in the synovial fluid of joints where it can cause painful arthritis (15). Epidemiologic studies have also shown that higher serum uric acid levels are associated with increased risk of hypertension and chronic kidney disease in adults (21, 44), as well as hypertension (24, 26, 44) and metabolic syndrome in children (28). Therefore, identification of new environmental risk factors for elevated uric acid, especially in children, may have implications for future cardiovascular disease prevention through earlier interventions to limit PFC exposure in children.

An association between PFC exposure and elevated serum uric acid levels has already been reported in adults from studies in populations exposed to very high levels of

Table 3. Association Between Plasma PFOA and PFOS Levels and Hyperuricemia (>6 mg/dL), NHANES, 1999–2008

Plasma PFC Level	No. at Risk	Hyperuricemia, Weighted %	Unadjusted Odds Ratio	95% CI	Multivariable-adjusted Odds Ratio[a]	95% CI
PFOA[b]						
Quartile 1	437	16.4	1	Referent	1	Referent
Quartile 2	462	21.3	1.42	0.97, 2.07	0.94	0.58, 1.53
Quartile 3	434	21.1	1.56	1.07, 2.28	1.01	0.62, 1.63
Quartile 4	439	27.6	2.77	1.99, 3.88	1.62	1.10, 2.37
P_{trend}			<0.0001		0.0071	
Log-transformed PFOA	1,772	21.6	2.22	1.69, 2.93	1.59	1.19, 2.13
PFOS[c]						
Quartile 1	444	15.9	1	Referent	1	Referent
Quartile 2	437	21.0	1.23	0.89, 1.70	1.17	0.80, 1.72
Quartile 3	448	20.5	1.18	0.84, 1.67	1.18	0.74, 1.87
Quartile 4	443	30.7	1.71	1.24, 2.36	1.65	1.10, 2.49
P_{trend}			0.0030		0.0221	
Log-transformed PFOS			1.37	1.14, 1.65	1.37	1.06, 1.76

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; PFC, perfluoroalkyl chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

[a] Adjusted for age (years), sex (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), body mass index categories (underweight, healthy weight, overweight, obese), annual household income categories, moderate activity (absent, present), total cholesterol (mg/dL), and serum cotinine (ng/mL).

[b] Plasma PFOA quartiles: quartile 1 (<2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), and quartile 4 (>5.4 ppb).

[c] Plasma PFOS quartiles: quartile 1 (<10.7 ppb), quartile 2 (10.7–16.5 ppb), quartile 3 (16.6–25.5 ppb), and quartile 4 (>25.5 ppb).

PFCs (27). However, clearance of PFCs in population-based studies in humans has been found to be concentration dependent. A recent study (33) examining PFOA clearance in a community-based sample ($n = 1,573$) found that PFOA's half-life was much shorter (2.9 years) in highly exposed participants than in those exposed at lower levels (8.5 years). Therefore, studying the putative PFC–uric acid association in lower-exposure groups is also important. In this context, using the NHANES data, Shankar et al. (45) examined the relationship between increasing quartiles of PFCs and hyperuricemia after controlling for potential confounders. Compared with subjects in quartile 1 (referent), those in quartile 4 had multivariate odds ratios for hyperuricemia of 1.97 (95% confidence interval (CI): 1.44, 2.70) for PFOA and 1.48 (95% CI: 0.99, 2.22) for PFOS. However, ours is the first study to examine the association between PFC exposure and serum uric acid levels in children. Consistent with previous studies in adults, we found that higher levels of PFOA and PFOS in blood are related to hyperuricemia in children, independent of major confounding factors.

Our results are also analogous to other recently published studies on the metabolic and other effects of PFC exposure in children. Using the community-based C8 Health Project data ($n = 12,476$), a population exposed to high levels of PFOA but not PFOS, Frisbee et al. (46) found a significant positive association between PFOA and PFOS exposure and dyslipidemia in children. In a cross-sectional, population-based study ($n = 571$), Hoffman et al. (47) uncovered a modest association between both PFOA (odds ratio = 1.12, 95% CI: 1.01, 1.23) and PFOS (odds ratio = 1.03, 95% CI: 1.01, 1.05) and attention deficit hyperactivity disorder in children.

The observed association between serum PFCs and uric acid levels is biologically plausible. One possibility is that PFCs may compete with uric acid for organic anion transporters 1 and 3, responsible for renal tubular secretion of uric acid (48), and therefore may result in reduced urinary excretion of uric acid. Alternatively, PFCs may be related to increased oxidative stress, which may subsequently result in increased levels of serum uric acid (49, 50). However, there is a need for more mechanistic animal studies to further clarify the biological mechanisms underlying our observed association.

This study's strengths include its relatively large sample size, nationally representative nature, availability of detailed data on confounders, and standardized, high quality data collection. The primary limitation is the study's cross-sectional nature, which prohibits drawing conclusions about the temporal nature of the PFC–serum uric acid association. Second, because the measurements of PFCs were made in a spot urine sample, we may not have been able to capture changes in serum PFOA or PFOS concentration in response to recent changes in exposure. This limitation may have caused some misclassification, and therefore it is possible that our results may be over- or underestimated. Future

studies should include multiple measures of PFCs over time in order to limit exposure misclassification.

In summary, we found that serum PFC levels were positively associated with hyperuricemia in a representative, multiethnic sample of US children. The association was present even after adjustment for age, sex, race/ethnicity, body mass index, annual household income, physical activity, serum total cholesterol, and serum cotinine. Future prospective studies are needed to confirm or disprove our findings.

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(Appendix follows)

Appendix Table 1. Association Between Serum PFOA and PFOS Levels and Serum Uric Acid Levels, NHANES, 1999–2008

Plasma PFC Level	Sample Size	Unadjusted Mean Change in Serum Uric Acid, mg/dL	95% CI	Multivariable-adjusted Mean Change in Serum Uric Acid, mg/dL[a]	95% CI
PFOA[b]					
Quartile 1	437	0	Referent	0	Referent
Quartile 2	462	0.23	0.09, 0.38	0.02	−0.11, 0.14
Quartile 3	434	0.27	0.10, 0.44	0.03	−0.11, 0.17
Quartile 4	439	0.66	0.50, 0.82	0.30	0.16, 0.43
P_{trend}		<0.0001		0.0001	
Log-transformed PFOA		0.43	0.32, 0.53	0.20	0.11, 0.29
PFOS[c]					
Quartile 1	444	0	Referent	0	Referent
Quartile 2	437	0.08	−0.07, 0.23	0.02	−0.11, 0.16
Quartile 3	448	0.11	−0.03, 0.26	0.09	−0.05, 0.22
Quartile 4	443	0.22	0.05, 0.39	0.12	−0.02, 0.26
P_{trend}		0.0147		0.0589	
Log-transformed PFOS		0.14	0.05, 0.23	0.09	0.02, 0.17

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; PFC, perfluoroalkyl chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

[a] Adjusted for age (years), sex (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), body mass index categories (underweight, healthy weight, overweight, obese), annual household income categories, moderate activity (absent, present), total cholesterol (mg/dL), serum cotinine (ng/mL), mother smoked when pregnant (absent, present), and anyone smoke inside home (absent, present).

[b] Plasma PFOA quartiles: quartile 1 (<2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), and quartile 4 (>5.4 ppb).

[c] Plasma PFOS quartiles: quartile 1 (<10.7 ppb), quartile 2 (10.7–16.5 ppb), quartile 3 (16.6–25.5 ppb), and quartile 4 (>25.5 ppb).