ORIGINAL RESEARCH

No association between perfluoroalkyl chemicals and hypertension in children

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Background: Hypertension is a leading cause of cardiovascular disease worldwide. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are perfluoroalkyl chemicals (PFCs) used in the manufacture of common consumer products and detected in the blood of the majority of Americans. Emerging biological data suggest that PFC exposure may have a role in the development of hypertension. However, the association between PFCs and hypertension has not yet been explored in humans. Therefore, we examined this association in a representative sample of US children.

Methods: A cross-sectional study was performed on 1,655 children from the National Health and Nutrition Examination Survey, 1999–2000 and 2003–2008. The main outcome of interest was hypertension, defined as age, height, and sex specific systolic and/or diastolic blood pressure level at the 95th percentile.

Results: We found no association between serum levels of PFOA and PFOS and hypertension in either unadjusted or multivariable-adjusted analyses controlling for age, sex, race-ethnicity, body mass index, annual household income, moderate activity, total serum cholesterol, and serum cotinine. Compared with the lowest quartile, the multivariable-adjusted odds ratio (95% confidence interval) of hypertension in the highest quartile of exposure was 0.69 (0.41–1.17) for PFOA and 0.77 (0.37–1.61) for PFOS (all P-trend values >0.30).

Conclusion: Our findings indicate that exposure to PFOA or PFOS is not significantly associated with hypertension in children at the lower PFC exposure levels typical of the general population.

Keywords: perfluorooctanoic acid, perfluorooctane sulfonate, perfluoroalkyl chemicals, blood pressure, children

Introduction

Perfluoroalkyl chemicals (PFCs) are detectable in the blood of more than 98% of the US population.[1] They 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.[2,3] PFCs are found in surfactants, lubricants, polishes, paper and textile coatings, food packaging, and fire-retarding foams, among many other consumer products. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are two of the most studied PFCs.

Hypertension is present in 29.0% of the adult US population and 3.2% of adolescents aged 11–17 years.[4] It is also the leading cause of cardiovascular disease worldwide.[5] Hypertension accounted for 56.5% of all-cause mortality in 2006, and death rates from hypertension increased by 19.5% from 1996 to 2006.[6] While traditional

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factors such as weight gain,[7,8] smoking,[9] and lack of physical activity[10] have been shown to be positively associated with hypertension, emerging literature suggests a role for common environmental exposures, including other manmade organic compounds,[11–15] in the development of hypertension.

A positive association between exposure to PFCs and hypertension is plausible. In a 2012 study, PFOA was reported to be linked to pregnancy-induced hypertension; this represents the only known epidemiologic study examining the association between PFOA and any form of high blood pressure.[16] However, PFCs such as PFOA and PFOS have been linked to higher cholesterol levels,[17] hyperuricemia,[18,19] metabolic syndrome,[20] insulin resistance,[20] and high serum gamma-glutamyl transpeptidase in previous epidemiologic studies,[21–24] all of which are factors reported to be independently related to hypertension.[18,25–28] In vitro studies have shown PFC exposure to be associated with oxidative stress[29,30] and endothelial dysfunction.[31,32] To our knowledge, the association between PFCs and hypertension has not been explored in children. Therefore, we sought to examine the association between PFCs and blood pressure levels in children using data from the nationally representative National Health and Nutrition Examination Survey (NHANES).

Materials and methods
Study population

This study uses 8 years of merged data from the NHANES, years 1999–2000, 2003–2004, 2005–2006, and 2007–2008. PFC data were not available for years 2001–2002. Data collection methods for NHANES have been published and are available online.[33] NHANES included a stratified multistage probability sample, representative of the noninstitutionalized civilian US population. 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 Service. The survey also includes biomonitoring for select environmental chemicals, including PFCs, 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 blood pressure, and the study sample consisted of children 18 years of age and younger who took part in both the interview and examination components. Because PFC levels are not sampled for children under the age of 12 years, the age range for this study was children 12–18 years (n=1,788). We additionally excluded those with missing values for covariates used in the multivariable model, including age, sex, race-ethnicity, annual household income, physical activity, total serum cholesterol, and serum cotinine (n=133). The final sample size of children included in this analysis was n=1,655.

Main outcome of interest: blood pressure

The main outcome of interest was systolic and diastolic blood pressure and the presence of hypertension. Blood pressure was measured in the examination component of the survey. The mean of up to three blood pressure readings was used for both systolic and diastolic blood pressure. Seated blood pressure was taken by a physician using a mercury sphygmomanometer following 5 minutes of rest according to American Heart Association and JNC7 (Seventh Report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) guidelines.[34,35] Details of blood pressure measurement and quality control procedures are available online.[36] Subjects were considered hypertensive if they had an average blood pressure level at the 95th percentile or greater, adjusted for age, height, and sex, as recommended by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.[37,38]

Exposure measurements

Sex, age, race/ethnicity, education level, physical activity, and annual household income were assessed by a standardized interview. Body mass index was calculated using the formula weight (kg)/height (m^2). Moderate physical activity was defined as participation in any moderate recreational physical activity. 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.[39] Briefly, serum total cholesterol was measured enzymatically. Perfluoroalkyl chemicals were measured in serum by the National Center for Environmental Health using automated solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry. Our study focused on PFOA and PFOS, two specific PFCs. Both were detected in the serum of over 98% of participants; values below the limit of detection were reported by NHANES as the limit of detection divided by the square root of 2.[39]

Statistical analysis

Serum PFOA and PFOS were analyzed as continuous and categorical variables. For analysis as a continuous variable, PFC values were log-transformed (base e) to correct skewed distributions. For analysis as a categorical variable, we categorized PFOA and PFOS into quartiles of increasing exposure. Linear regression models were used to examine mean change in blood pressure with increasing category of PFC, using the lowest PFC quartile as the referent. We ran two nested models: unadjusted and multivariable-adjusted, controlling for age (<18 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), and serum total cholesterol (mg/dL). We also ran unadjusted and multivariable-adjusted logistic regression models to calculate the odds ratio (95% confidence interval) of hypertension for each PFC quartile, using quartile 1 as the referent. Trends in the odds ratio of hypertension across increasing serum PFC quartiles were determined by modeling the PFCs as ordinal variables. In a series of supplemental analyses, we explored the possibility of a nonlinear relationship between PFOA, PFOS, and blood pressure levels. We conducted nonlinear regression modeling using the NLIN procedure.[40,41]

Sample weights that account for unequal probabilities of selection, oversampling, and nonresponse in the NHANES survey were applied for all analyses, as recommended by the National Center for Health Statistics.[42] Analyses were conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA) software. Standard errors were estimated using the Taylor series linearization method.

Results

Characteristics of the study population (n=1,655) are shown in Table 1. Nearly half of the study population was female and the mean age of 15.1 years had a standard error of only ±0.1. The majority of the sample was non-Hispanic White, but Blacks (14.3%) and Mexican Americans (11.8%) were represented as well. Nearly half of study participants fell into the highest household income category and almost 37.0% of the children were overweight or obese.

Our first multivariate analysis consisted of linear regression modeling to study the association between increasing

Table 1 Characteristics of study population

Characteristics	Percentage or mean value ± standard error
Unweighted sample size	1,655
Age, years	15.1±0.1
Women, %	49.0
Race-ethnicity, %	
Non-Hispanic white	62.5
Non-Hispanic Black	14.3
Mexican American	11.8
Other	11.4
Annual household income	
Under $25,000	23.9
$25,000–$54,999	28.1
$55,000 and over	48.1
No moderate activity, %	17.9
Body mass index category, %	
Underweight	4.1
Normal weight	59.2
Overweight	18.2
Obese	18.5
Total cholesterol, mg/dL	159.7±1.1
Serum cotinine, ng/mL	15.0±1.7
Systolic blood pressure, mmHg	110.0±0.5
Diastolic blood pressure, mmHg	60.5±0.4
Hypertension, %	23.4
PFOA, ng/mL	4.4±0.1
PFOS, ng/mL	18.4±0.5

Abbreviations: PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

quartiles of serum PFOA and PFOS and the mean change in serum systolic (Table 2) and diastolic (Table 3) blood pressure level in mmHg. The association between PFCs and blood pressure was not significant in either model (all *P*-trend values >0.30). The relationship was also not significant in either model for log-transformed PFOA or PFOS.

In addition, we also analyzed the putative association between increasing quartiles of serum PFOA and PFOS and the presence of hypertension using logistic regression models (Table 4). Results were similar to those of the linear regression analysis in that we did not observe an association between PFOA or PFOS and hypertension in any model (all *P*-trend values >0.30). The relationship was also not significant in either model for log-transformed PFOA or PFOS.

Nonlinear regression analyses were consistent with linear and logistic regression modeling. No association was observed between PFOA or PFOS and blood pressure levels.

Discussion

We did not find a positive association between exposure to PFOA and PFOS and elevated blood pressure levels in a nationally representative sample of children.

Table 2 Association between serum PFOA, PFOS levels, and systolic blood pressure

Plasma PFC level	Sample size (n)	Unadjusted mean change in blood pressure in mmHg (95% CI)	Multivariable-adjusted mean change in blood pressure in mmHg (95% CI)[‡]
PFOA*			
Quartile 1	398	0 (referent)	0 (referent)
Quartile 2	433	2.51 (0.17, 4.85)	0.60 (−1.39, 2.60)
Quartile 3	410	1.63 (−0.99, 4.25)	0.21 (−2.14, 2.57)
Quartile 4	414	1.43 (−1.14, 4.00)	−0.89 (−3.06, 1.28)
P-trend		0.4808	0.3550
Log-transformed PFOA		0.01 (−1.70, 1.71)	−1.22 (−2.74, 0.31)
PFOS[†]			
Quartile 1	413	0 (referent)	0 (referent)
Quartile 2	413	0.84 (−1.13, 2.80)	−0.25 (−1.87, 1.36)
Quartile 3	413	0.70 (−1.64, 3.04)	0.29 (−1.76, 2.34)
Quartile 4	416	0.66 (−1.80, 3.12)	−0.11 (−2.07, 1.85)
P-trend		0.6230	0.9210
Log-transformed PFOS		0.26 (−1.16, 1.69)	−0.04 (−1.19, 1.12)

Notes: *Plasma PFOA quartiles: quartile 1 (<2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), quartile 4 (>5.4 ppb); [†]plasma PFOS quartiles: quartile 1 (<10.8 ppb), quartile 2 (10.8–16.6 ppb), quartile 3 (16.7–25.5 ppb), quartile 4 (>25.5 ppb); [‡]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).
Abbreviations: CI, confidence interval; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFC, perfluoroalkyl chemicals; ppb, parts per billion.

Multivariable models controlled for age, sex, race-ethnicity, body mass index, annual household income, physical activity, serum total cholesterol levels, and serum cotinine levels. Our analysis contributes to the extant literature by being the first to examine the association between PFC exposure and hypertension in humans.

Hypertension is a common condition which is also a strong, independent risk factor for cardiovascular disease.[5] The pathophysiology of hypertension is incompletely understood, but several factors have been implicated, including psychosocial stress, excessive sodium-retaining hormone production, increased sympathetic nervous system activity, and vasodilator deficiency.[43] Hypertension remains a major public health problem despite substantial advances in our understanding of its etiology, pathophysiology, and effective treatment.[44]

No previous study has examined the association between PFCs and hypertension. In relation to our hypothesis, one

Table 3 Association between serum PFOA, PFOS levels, and diastolic blood pressure

Plasma PFC level	Sample size	Unadjusted mean change in blood pressure in mmHg (95% CI)	Multivariable-adjusted mean change in blood pressure in mmHg (95% CI)[‡]
PFOA*			
Quartile 1	398	0 (referent)	0 (referent)
Quartile 2	433	−0.27 (−2.27, 1.73)	−0.06 (−2.11, 1.99)
Quartile 3	410	1.10 (−0.72, 2.93)	1.25 (−0.53, 3.03)
Quartile 4	414	0.32 (−1.64, 2.28)	0.33 (−1.71, 2.37)
P-trend		0.4156	0.4205
Log-transformed PFOA		0.25 (−1.11, 1.61)	0.36 (−0.99, 1.71)
PFOS[†]			
Quartile 1	413	0 (referent)	0 (referent)
Quartile 2	413	0.38 (−1.73, 2.48)	0.42 (−1.61, 2.45)
Quartile 3	413	1.39 (−0.86, 3.64)	0.99 (−1.20, 3.17)
Quartile 4	416	0.51 (−1.41, 2.43)	0.17 (−1.95, 2.29)
P-trend		0.4310	0.7503
Log-transformed PFOS		0.83 (−0.36, 2.02)	0.47 (−0.81, 1.74)

Notes: *Plasma PFOA quartiles: quartile 1 (<2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), quartile 4 (>5.4 ppb); [†]plasma PFOS quartiles: quartile 1 (<10.8 ppb), quartile 2 (10.8–16.6 ppb), quartile 3 (16.7–25.5 ppb), quartile 4 (>25.5 ppb); [‡]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).
Abbreviations: CI, confidence interval; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFC, perfluoroalkyl chemicals; ppb, parts per billion.

Table 4 Association between plasma PFOA, PFOS levels, and hypertension

Plasma PFC level	Number at risk	Hypertension weighted %	Unadjusted odds ratio (95% CI)	Multivariable-adjusted odds ratio (95% CI)‡
PFOA*				
Quartile 1	398	20.4	1 (referent)	1 (referent)
Quartile 2	433	24.7	1.28 (0.77, 2.15)	0.89 (0.53, 1.49)
Quartile 3	410	24.8	1.29 (0.70, 2.38)	0.96 (0.53, 1.73)
Quartile 4	414	23.0	1.17 (0.66, 2.07)	0.69 (0.41, 1.17)
P-trend			0.6522	0.2477
Log-transformed PFOA			1.03 (0.70, 1.52)	0.76 (0.53, 1.10)
PFOS†				
Quartile 1	413	22.6	1 (referent)	1 (referent)
Quartile 2	413	26.9	1.26 (0.75, 2.11)	0.99 (0.55, 1.78)
Quartile 3	413	20.3	0.88 (0.47, 1.63)	0.73 (0.36, 1.48)
Quartile 4	416	22.9	1.02 (0.52, 1.99)	0.77 (0.37, 1.61)
P-trend			0.7527	0.3625
Log-transformed PFOS			0.96 (0.70, 1.32)	0.83 (0.58, 1.19)

Notes: *Plasma PFOA quartiles: quartile 1 ($<$2.9 ppb), quartile 2 (2.9–4.0 ppb), quartile 3 (4.1–5.4 ppb), quartile 4 ($>$5.4 ppb); †plasma PFOS quartiles: quartile 1 ($<$10.8 ppb), quartile 2 (10.8–16.6 ppb), quartile 3 (16.7–25.5 ppb), quartile 4 ($>$25.5 ppb); ‡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).
Abbreviations: CI, confidence interval; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFC, perfluoroalkyl chemicals; ppb, parts per billion.

recent study analyzed the relationship between PFCs and pregnancy-induced hypertension, a condition of high blood pressure seen in pregnancy that can lead to potentially severe health risks to the mother as well as to the fetus.[16] This study was conducted by a team of scientists who were appointed by the court to study the health effects of PFC exposure following litigations between DuPont Chemical Works and more than 69,000 plaintiffs exposed to high levels of PFOA in drinking water due to a chemical leak from this plant. This panel of scientists has recently publicly announced several findings, including a positive association between PFOA and pregnancy-induced hypertension; however, these findings have not yet been subjected to scientific peer review. In addition, there is indirect evidence supporting our hypothesis of a putative association between PFC exposure and hypertension.

Several factors that are known to be associated with increased risk of hypertension,[25–27] including elevated cholesterol,[28] hyperuricemia,[19] oxidative stress,[29,30] endothelial dysfunction,[31] insulin resistance,[20] weight gain,[45] and elevated serum gamma-glutamyl transpeptidase,[29] have been shown to be independently related to PFC exposure. Low-level exposure to PFCs has also been shown to be significantly associated with other health outcomes such as dyslipidemia,[24] hyperuricemia,[46] thyroid disease,[47] and changes in liver enzymes,[20] and therefore may be deleterious to public health even in the absence of an association with hypertension. Finally, high-level PFC exposure is known to be linked to a host of negative health outcomes, including dyslipidemia,[17]

hyperuricemia,[19] early menopause,[48] and osteoarthritis,[49] among others. Despite these leads, our study did not find an association between PFC exposure and the presence of hypertension in a multiethnic, representative sample of children.

In a recent population-based study, Seals et al[50] 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 that PFCs are present in the blood of the majority of Americans only at low levels,[3] the current study of the relationship between PFC exposure and hypertension in the representative NHANES sample renders our results to be more generalizable and relevant than studies from high PFC exposure groups, such as the study linking PFCs to pregnancy-induced hypertension.[16] Also, children are an ideal sample in which to study environmental cardiovascular risk factors because there is now an emerging consensus that the development of cardiovascular disease in adulthood is preceded by metabolic changes occurring in childhood,[51–53] and compared with adults, children tend to 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.

Other strengths of our study include its relatively large sample size, availability of detailed data on confounders, and standardized, high-quality data collection. The primary limitation is the cross-sectional nature of the study, which

prohibits drawing conclusions about the temporal nature of the PFC-blood pressure association.

In summary, we found no association between serum PFC levels and blood pressure in a representative, multiethnic sample of US children. Results were consistent across regression models in separate analyses for PFOA and PFOS. Future research should be conducted to confirm or disprove our results.

Acknowledgment

Disclosure

The authors report no conflicts of interest related to this paper.

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