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# Perfluoroalkyl acids, hyperuricemia and gout in adults: Analyses of NHANES 2009–2014

**Franco Scinicariello**[a,*], **Melanie C. Buser**[a], **Lina Balluz**[a], **Kimberly Gehle**[a], **H. Edward Murray**[a], **Henry G. Abadin**[a], **Roberta Attanasio**[b]

[a]Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA, 30341, USA

[b]Department of Biology, Georgia State University, Atlanta, GA, USA

## Abstract

**Background:** Previous studies have reported a positive association of perfluoralkyl acids (PFAAs), including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), with hyperuricemia. The objective of the study is to investigate whether there is an association between concurrent serum levels of several PFAAs and gout, serum uric acid (SUA) or hyperuricemia in the U.S. adult population as represented by the National Health and Nutrition Examination Survey (NHANES) 2009–2014 sample ($n$ = 4917). The PFAAs investigated include PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS) and PFOS.

**Methods:** This cross-sectional study used multivariate logistic regressions to analyze the association of single PFAAs with hyperuricemia and self-reported gout; the association with SUA was analyzed by multivariate linear regression. Analyses were adjusted for race/ethnicity, age, sex, education, alcohol consumption, smoking, serum cotinine, BMI, diabetes, hypertension, chronic kidney disease, and SUA (for gout only).

**Results:** Higher quartile values of serum PFOA and PFHxS were associated with increased odds of self-reported gout. There was a positive association of SUA with increased levels of PFOA, PFNA, PFOS, PFHxS and PFDA. Higher quartile values of PFOA, PFNA, and PFHxS were associated with higher odds of hyperuricemia.

[*]Corresponding author. Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, 4770 Buford Hwy, MS S102-1, Atlanta, GA, 30341, USA. fes6@cdc.gov (F. Scinicariello).

CRediT authorship contribution statement

**Franco Scinicariello:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Melanie C. Buser:** Software, Writing - original draft, Visualization. **Lina Balluz:** Software, Writing - original draft, Visualization. **Kimberly Gehle:** Visualization, Writing - review & editing. **H. Edward Murray:** Visualization, Writing - review & editing. **Henry G. Abadin:** Visualization, Writing - review & editing. **Roberta Attanasio:** Software, Visualization, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2020.127446.

**Conclusions:** In this population-based cross-sectional analysis, we found an association between selected PFAAs and self-reported gout. We also confirmed previous reports of an association between several PFAAs and hyperuricemia. Our study suggests that exposure to PFAAs may be a risk factor for hyperuricemia and gout.

**Keywords**

Gout; Hyperuricemia; NHANES; Perfluoralkyl acids; Uric acid

## 1. Introduction

Gout is a common form of arthritis that results from the deposition of urate (monosodium urate monohydrate) crystals in joints, leading to an acute inflammatory response, or in soft tissues (e.g., cartilage) without causing inflammation (Dalbeth et al., 2016). The prevalence of gout has been increasing over the past few decades, and now affects around 4% of US adults (Lawrence et al. 2008; Zhu et al., 2011). A recent systematic review of the economic burden of gout found that gout patients incur substantial direct and indirect costs, with some estimates of annual gout-related costs exceeding $6000 per person (Rai et al., 2015). Moreover, increases in serum uric acid and gout are associated with cardiovascular and renal diseases, and the prevalence of these comorbidities increases with gout duration (Bardin and Richette, 2017). The pathological progression of gout has been of increasing interest in the past years (reviewed in Dalbeth et al., 2016). Increased levels of serum uric acid (SUA) increases the risk of gout; however, only a minority of people with hyperuricemia develop gout (Chhana et al., 2015). Uric acid is a product of the metabolism of purines, which are found in many foods and in human tissue (Mandal and Mount, 2015). Hyperuricemia may occur as a result of overproduction from hepatic metabolism and cell turnover, from renal and/or extra-renal underexcretion, or from higher purine intake. Underexcretion of uric acid is the dominant cause of hyperuricemia in patients with gout (Perez-Ruiz et al., 2002), with genetic polymorphisms in renal urate transporter playing an important role (Robinson , 2018).

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a large group of man-made chemicals that have been used extensively as ingredients or intermediates of surfactants and surface protectors for a wide range of industrial and consumer applications, as well as being used in fire-fighting foams (ATSDR, 2018; Buck et al., 2011). The general population is exposed to these substances through contaminated drinking water, food products, dust, and consumer products that contain PFAS (ATSDR, 2018; Calafat et al., 2007). A subset of PFAS is represented by the perfluoroalkyl acids (PFAAs), such as perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS). More than 95% of the general U.S. population has detectable serum levels of PFAAs (ATSDR, 2018). These five PFAAs are highly persistent in the environment, are readily absorbed following inhalation or oral exposure and are not metabolized in humans or animals. Thus, there is a substantial bioaccumulation following exposure. Additionally, PFAAs have high protein binding in the blood, which plays a critical role in bioaccumulation. Evidence in humans and animals supports that perfluoroalkyls in plasma bind to serum albumin; additionally, several PFAAs

have been reported to bind to other human serum binding proteins, including plasma gamma-globulin, alpha-globulin, alpha-2 macro-globulin, transferrin, and beta-lipoproteins (Butenhoff et al., 2012; Chen and Guo, 2009; Ohmori et al., 2003). Only free (unbound) PFAAs are available for redistribution, excretion, and renal absorption. Therefore, the interaction of PFAAs binding to proteins plays a critical role in bioaccumulation. With the tissue environment highly favoring protein binding, in humans, the half-lives of these PFAAs may be upwards of 20 years (ATSDR, 2018). The elimination half-life of PFOA in humans estimated to be 3.5 years and for PFOS 4.8 years (Olsen et al., 2007). In recent study from a community with residential exposure to PFAS in contaminated water the half-life has been estimated at 15.5 years (Worley et al., 2017).

The association between serum PFAA levels and serum uric acid levels in adults has been investigated previously. Occupational studies have reported associations between PFOA and serum uric acid (Costa et al., 2009; Sakr et al., 2007), and a study on a highly exposed community reported increased risk of hyperuricemia associated with higher levels of PFOA and PFOS (Steenland et al., 2010). Studies on the general population, including analyses utilizing the NHANES database, have reported similar associations between several PFAS and SUA or hyperuricemia risk in both adolescents and adults (Geiger et al., 2013; Gleason et al., 2015; Kataria et al., 2015 Qin et al., 2016; Shankar et al., 2011). However, to date the potential association of PFAAs and gout has not been investigated. The present study examines the concurrent relationship between several serum PFAAs – PFOA, PFNA, PFDA, PFOS, and PFHxS – and gout in adults 20 years of age and older. Furthermore, we add to existing evidence of the association between PFAAs and SUA concentrations, using population data from NHANES 2009–2014.

## 2. Methods

### 2.1. Study population

NHANES is a cross-sectional, nationally representative survey of the non-institutionalized civilian population of the United States conducted annually by the Centers for Disease Control and Prevention's National Center for Health Statistics (CDC/NCHS) (Johnson et al., 2013). For our study, we merged the publicly available files for the NHANES 2009—2010, 2011—2012, and 2013—2014 cycles using NCHS recommended methods (Johnson et al., 2013). The survey employs a multistage stratified probability sample.

NCHS-trained professionals conducted interviews in participants' homes; physical and laboratory examinations, including blood and urine collection, were conducted at mobile exam centers. All procedures were approved by the NCHS Research Ethics Review Board (Continuation of Protocol #2011—17 http://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants provided written informed consent. For our analysis, we included adults (ages 20 years and older) who had biological measurements for PFAAs (n = 5192) and information regarding the covariates included in the model (discussed below) for a final sample size of 4917 individuals.

### 2.2. Perfluoroalkyl substances (PFAS) measurements

Serum PFAS were measured by the CDC's National Center for Environmental Health (NCEH), Division of Laboratory Sciences (DLS). CDC/NCEH/DLS analyzed the serum levels of fourteen different PFAS. Among them, five PFAAs which were detected in 95% of the serum samples, such as PFOA, PFNA, PFDA, PFOS and PFHxS, were included in our analyses. We summed the concentrations of the branched and linear isomers to obtain total PFOA and PFOS concentrations (Ye et al., 2018). These compounds were measured using automated solid-phase extraction coupled to reverse-phase high-performance liquid chromatography/tandem mass spectrometry (https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/PFAS_H_MET.pdf). The limits of detection (LODs) ranged from 0.08 to 0.2 ng/mL for the PFAAs included in the analysis. For concentrations less than the LOD, a value equal to the limit of detection divided by the square root of two was used.

### 2.3. Outcomes

Serum samples were collected from study participants and stored at −30 °C until shipped to CDC/NCEH/DLS for testing. SUA was measured as part of the routine serum biochemistry profile using the Beckman Coulter UniCel® DxC800 with a timed endpoint method (https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/BIOPRO_H_MET_URIC_ACID.pdf). Hyperuricemia was defined as SUA levels ≥7 mg/dL for males and ≥6 mg/dL in females (Feig et al., 2008). The presence of gout was obtained from medical condition questionnaire, based on the self-reported answer to: "Has a doctor or other health professional ever told you that you have gout?" Based on the answer to the question "How old you were when first told you had gout?', we calculated the time in year between the actual age of the NHANES participants minus the age of the participants when gout was first diagnosed by a health professional. The average geometric mean diagnosis of gout was done 9.63 years with an average mean of 13.74 years (95% CI: 11.65, 15.83 years) before the blood was collected for PFAAs analyses.

### 2.4. Covariates

The following *a priori* covariates were included in the analyses: age (years), race/ethnicity, sex, education, alcohol consumption, smoking status, serum cotinine, body mass index (BMI), diabetes, hypertension, and chronic kidney disease (CKD). Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican-American and other Hispanic), and other race/multiracial. Education was categorized as having completed less than high school, high school, or more than high school. Alcohol consumption (number of drinks consumed per week) and smoking status (self-reported current smoker, former smoker, or never smoker) were obtained from their respective questionnaires. Serum cotinine was natural log-transformed. BMI was obtained from the physical examination and was calculated by dividing measured weight (kg) by measured height ($m^2$). Participants were classified as having diabetes based on: 1) the "yes" answer to the questions: "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" or "now taking insulin" or "now taking diabetic pills", or; 2) their hemoglobin A1c was greater than or equal to 6.5%. or; 3) their fasting (8–24 h) plasma glucose was greater than or equal to 126 mg/dL. Participants were classified has

having hypertension if their systolic blood pressure was greater than or equal to 140 mmHg or diastolic blood pressure was greater than or equal to 90 mmHg, or they were currently taking medication to lower high blood pressure.

Chronic Kidney Disease (CKD) was defined as eGFR < 60 mL/min/1.73 $m^2$, and/or albuminuria (Webster et al., 2017). Estimated glomerular filtration rate (eGFR, mL/minute/1.73 $m^2$) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (1):

$$eGFR = 141 \times \min\left(\frac{Scr}{k}, 1\right) \times \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159 [if\ non\ Hispanic\ black] \quad (1)$$

where Scr is serum creatinine (mg/dL), $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/$\kappa$ or 1, and max indicates the maximum of Scr/$\kappa$ or 1 (Levey et al., 2009). Albuminuria was defined as albumin-to-creatinine ratio (ACR) above 30 mg/g (Webster et al., 2017).

### 2.5. Statistical methods

All analyses were performed using the chemical-specific subsample weight as recommended by NCHS. Weights for combined NHANES survey cycles were calculated according to NHANES guidelines (Johnson et al., 2013). PFAAs were categorized via weighted quartile, with cutoffs based on the weighted distribution of the PFAAs concentration in the studied population. Weighted Pearson correlation coefficients of log-transformed PFAAs concentrations and related p-values were calculated in SAS. SAS 9.3 (SAS Institute, Cary, NC) and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) were used to account for the NHANES complex sample design. We used multivariable linear regression to calculate adjusted β-coefficients and 95% confidence intervals (CIs) for the associations between SUA and serum PFAAs levels. We used multivariable logistic regression to calculate adjusted odds ratios (ORs) and 95% CIs for the associations between gout and hyperuricemia with serum PFAAs levels. Statistical tests for linear trends were conducted by modeling quartiles as an ordinal variable using integer values. All models were adjusted for race/ethnicity, age, sex, education, alcohol consumption, smoking, serum cotinine, BMI, diabetes, hypertension, and chronic kidney disease; when modeling self-reported gout as the outcome, serum uric acid was also entered as a covariate.

As a supplemental analysis, all models were run excluding individuals that fulfill the criteria of chronic kidney disease (CKD), and eGFR was entered in the model as continuous variable. Reverse causality represents a major limitation in studies investigating the association between biomarkers of renal function and serum levels of substances, so we chose to restrict our study to individuals with normally functioning kidneys in order to mitigate this potential effect. While the supplemental analysis cannot rule out the so called “reverse causality”, it may lend support to a true association between exposure and outcome. Moreover, to further characterize the shape of the relationship between each PFAAs and SUA we used each PFAAs variable as restricted cubic spline. We used a modified SAS

macro written by Desquilbet and Mariotti (2010) to account for NHANES weight and sample design, and the knots used for restricted cubic spline were placed at the 5th, 35th, 65th and 95th percentiles or 10th, 50th and 90th percentiles as recommended by Harrell (2010).

## 3. Results

Table 1 illustrates the weighted characteristics of adult participants (20 years of age and older) from NHANES 2009–2014 included in this analysis. Among the study population (n = 4917), the geometric mean age was 44.1 years and 51.6% were female. Non-Hispanic whites accounted for 67.8% of the total study group; 10.7% were non-Hispanic blacks, 14.5% were Mexican-American and other Hispanic, and 7.0% were “other race/ethnicity”. 56.6% of participants reported never smoking, 26.6% reported no alcohol use, and 62.1% reported completing more than high school education. The geometric mean (GM) of serum cotinine was 0.24 ng/mL, the GM serum creatinine was 0.85 mg/dL, and the GM BMI was 28.16. The percentage of participants reporting chronic kidney disease (CKD), diabetes, and hypertension were 612.8%, 13.1%, and 30.7%, respectively. The GM (SE) for SUA (mg/dL), eGFR (mL/minute/1.73 $m^2$), and ACR(mg/g) were 5.21 (0.03), 91.47 (0.49), and 8.15 (0.15), respectively. 3.8% of participants reported doctor-diagnosed gout, and 18.6% were classified as having hyperuricemia. The GM of PFOA, PFNA, and PFDA were 2.37 ng/mL, 0.92 ng/mL, and 0.23 ng/mL, respectively. The GM of PFOS and PFHxS were 6.98 ng/mL and 1.42 ng/mL, respectively (Table 1). Statistically significant correlations ($p < 0.001$) existed between the log-transformed concentrations of each PFAA (Table 2).

### 3.1. Serum uric acid (SUA)

Table 3 presents the multivariate linear regression analyses for the association of SUA with individual PFAA levels in adults (20 years of age and older). All five PFAAs were associated with increased serum uric acid and eGFR was entered in the model as continuous variable. In supplemental analyses restricted to participants without CKD, the statistically significant associations with increased SUA levels remained for all five PFAAs. (Table 4). Similarly, when the analyses were restricted to participants with CKD, a positive association was found between increased SUA and higher level of the PFAAs; the associations for PFOA and PFDA were not statistically significant (Table 5). Analyses using restricted spline performed either in all sample or stratified by the presence of CKD, showed similar nonlinear, positive statistically significant associations between increased PFAAs and SUA (Supplementary Figures 1–15), even in participants with CKD; PFOA was positively associated with SUA (Supplementary Figure 3).

### 3.2. Hyperuricemia

Table 3 presents the multivariate logistic regression analyses for the associations of individual PFAS levels and the odds of having hyperuricemia. Participants in the 4th quartile of PFOA (OR [95% CI]: 1.81 [1.29, 2.55]), the 3rd and 4th quartiles of PFNA (OR [95% CI]: 1.55 [1.20, 2.01] and 1.65 [1.23, 2.22], respectively), the 4th quartile of PFOS (OR [95% CI]:1.45 [1.03, 2.03]), and the 4th quartile of PFHxS (OR [95% CI]: 1.51 [1.12, 2.03]) had statistically significant higher odds of having hyperuricemia compared to those in the

respective, referent quartiles. When analyses were restricted to participants without CKD, he statistically significant associations were maintained only between PFNA and PFOA and odds of having hyperuricemia (Table 4).

### 3.3. Gout

Table 3 presents the multivariate logistic regression analyses for the association of individual PFAS levels and the odds of self-report of having gout. Participants in the 3rd and 4th quartiles of PFOA had statistically significant increased odds of having gout (OR [95% CI]: 2.34 [1.32, 4.15] and 3.17 [1.68, 5.98], respectively). Additionally, participants in the 2nd, 3rd, and 4th quartiles of PFHxS had statistically significant increased odds of having gout (OR [95% CI]: 2.35 [1.20, 4.60], 2.24 [1.15, 4.36], and 2.76 [1.36, 5.62], respectively) compared to the lowest referent quartile. Higher levels of PFNA were associated with gout, but only those in 3rd quartile reached statistically significance. These statistically significant associations were maintained when analyses were restricted to participants without CKD (Table 4). Higher levels of PFDA was associated with higher odds of having gout only in the analyses restricted to participants without CKD (Table 4).

## 4. Discussion

To our knowledge, this is the first reported association of concurrent serum PFAAs with self-reported diagnosis of gout in adults (20 years of age and older) using a nationally representative survey of the adult US population. We found positive associations of PFOA and PFHxS with gout, which remained significant when analyses were restricted to participants with normal kidney function (eGFR ≥ 60 mL/min/1.73 $m^2$).

Although our findings on the relationship between SUA and PFAAs are consistent with previous studies in the general population, some of our findings are novel. In our analyses, all five single PFAAs were associated with increased SUA; moreover, PFOA, PFNA and PFHxS were associated with higher odds of having hyperuricemia. Gleason et al. (2015) investigated the association between PFOA, PFNA, PFHxS, and PFOS with SUA as well as liver enzymes using NHANES 2007–2010 in participants 12 years of age and older. All four natural-log-transformed perfluoroalkyl compounds were positively associated with SUA; logistic regression found that only PFOA (analyzed as quartiles) had a statistically significant association with high SUA. Shankar et al. (2011) reported an association of PFOA with uric acid and hyperuricemia in adult participants of NHANES 1999–2000 and 2003–2006, and PFOS was positively associated with increased SUA. Associations between serum PFOA and PFOS levels and SUA levels have also been reported in a study of highly exposed residents. Steenland et al. (2010) found a positive linear trend between SUA and serum PFOA and PFOS levels among 54,951 adults (≥20 years of age) participating in the C8 Health Project with mean serum PFOA and PFOS concentrations of 86.4 and 23.4 ng/mL, respectively. Furthermore, PFOA and PFOS levels were associated with statistically significant increased risk of hyperuricemia (Steenland et al., 2010).

This study adds to the growing body of literature suggesting the nephrotoxic potential of PFAS. The mechanism(s) of action by which PFASs may affect renal function has not been fully clarified, though several mechanisms have been suggested. After filtration by the

glomerulus, uric acid undergoes a series of reabsorption and secretion processes in the proximal tubule, resulting in net uric acid excretion that is typically 8–12% of the initially filtered uric acid load (Fathallah-Shaykh and Cramer, 2014). The extensive reabsorption in the proximal tubule is largely mediated by the uric acid reabsorption transporters found in the apical membrane of epithelial cells, which includes urate anion transporter 1 (URAT1) and organic anion transporter 4 (OAT 4). The small portion that is secreted is mediated by two categories of tubular urate excretion transporters that are responsible for the uptake and excretion of uric acid. The organic anion transporters OAT1 and OAT3, located in the basolateral membrane of epithelial cells, have been considered the primary candidates for the uptake of uric acid from the renal interstitial space into tubular epithelial cells. Several apical secretory transporters have been shown to transport urate *in vitro*, and, NPT4/SLC17A3 and NPT1/SLC17A1 are the renal apical secretory transporters with the most support for a role in the renal secretion of urate (reviewed in Hyndman et al., 2016). Similar to urate, PFASs are substrates for URAT1 and OAT4 (Nakagawa et al., 2009; Yang et al., 2010), as well as for OAT1 and OAT3 (Nakagawa et al., 2008; Han et al., 2012). Furthermore, it has been shown that PFAAs, such as PFOA and PFOS, decrease the expression of SLC17A1 mRNA (Ren et al., 2009), thus it may be plausible that the decreased production of the NPT1 transporter may ultimately result in decreased renal excretion of uric acid.

Additionally, it has been shown that PFOA is an inhibitor of the HNF4α pathway in HepG2 cells (Scharmach et al., 2012) and in human primary hepatocytes with inhibition of HNF1α-dependent pathway (Buhrke et al., 2015), which is primarily regulated by HNF4α (Lu et al., 2008). Recently, Beggs et al. (2016) showed that exposure of primary human hepatocytes to PFOA or PFOS caused a decrease in HNF4α protein. The transcription factors HNF1α and HNF4α are members of the nuclear receptor superfamily that are expressed in the liver, kidney, and intestine, and several studies indicate that they positively regulate the renal OAT1 and OAT3 gene (reviewed in Wang and Sweet, 2013). Therefore, another plausible mechanism by which the PFAAs may affect renal excretion of urate is through inhibition of HNF1α and HNF4α, resulting in lower expression of renal OAT1 and OAT3 genes.

Reverse causality is a major limitation of our study and may represent an alternate explanation of our findings: serum PFAAs could be higher simply because of reduced excretion, which may also explain the increased SUADhingra et al. (2017) in a study aimed at evaluating reverse causality in cross-sectional studies suggested that even if PFOA did not alter kidney function, “measured PFOA might still appear to be inversely associated with eGFR if preexisting decreased renal function affects PFOA excretion and hence serum levels.” In the absence of the ability to use modeled serum levels rather than measured serum levels as suggested by Dhingra et al. (2017), we restricted supplemental analyses to individuals with normal renal function (defined as eGFR ≥ 60 mL/min/1.73 $m^2$ and albumin-to creatinine ratio less or equal 30 mg/g, as well as in individuals with renal failure (defined as eGFR< 60 mL/min/1.73 $m^2$ and/or albumin-to creatinine ratio above 30 mg/g), in order to lessen the likelihood that preexisting decreased renal function was affecting PFAAs excretion. These supplemental analyses confirmed the positive associations found between PFAAs and SUA, hyperuricemia, or gout, suggesting that the results may indicate a true adverse effect rather than just a result of reverse causality. Similar conclusion was found by

Jain and Ducatman (2019) where they investigated the differences in associations between PFAS and uric acid across the stages of glomerular filtration.

The results of this study indicated that the association between PFAS and uric acid reverse in males with advanced renal failure, indicating that the association is not due to renal failure (Jain and Ducatman, 2019).

Another limitation is that the diagnosis of self-reported gout preceded the measurement of blood PFAS levels. However, among the participants that reported gout, the diagnosis by the doctor was done on average 13.74 years ago (95% CI: 11.65, 15.83). Since, the measured PFAAs have a very long half-lives, it may be that, at the time of diagnosis there is a likelihood that perfluoroalkyls exposure was much higher. In fact, the first population survey reporting measurement of perfluoroalkyls was the NHANES 1999–2000, and the reported geometric means for adults (20 years and older) were: 2.05 ng/mL for PFHxS, 0.573 ng/mL for PFNA, 5.16 ng/mL for PFOA, and 30.6 ng/mL for PFOS (CDC, 2009). The geometric mean of serum PFDA in NHANES 2005—2006 was 0.364 ng/mL (CDC, 2017). Except for PFNA, the mean serum PFAS levels were much higher in the general US population in 1999—2000 compared to those in this study.

Other limitations of this analysis include that this is a cross-sectional study that uses concurrent measures of exposure and outcome, so causality cannot be established. Furthermore, the use of a single serum measure may not reflect past exposure. However, these substances have long half-lives in humans, so exposure misclassification is less likely. Because many associations were evaluated, we cannot dismiss the possibility that the significant associations were observed by chance. Furthermore, while our study adjusted for several important covariates, there are other potential contributors to gout that we did not control for, including diet high in purines and use of medications that are known to influence serum uric acid levels.

## 5. Conclusion

Increases in serum uric acid and gout are associated with cardiovascular and renal diseases, and the prevalence of these comorbidities increases with gout duration. Because the prevalence of gout has been increasing over the past decades, it is important to understand potential risk factors associated with this disease. Our study suggests that exposure to PFAAs may be a predictive risk factor for hyperuricemia and gout; due to their persistent nature and long half-lives in humans, this makes them an important public health concern.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLAIMER: The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of CDC/ATSDR.

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## HIGHLIGHTS

- We examined the association of perfluoroalkyls acids with gout and uric acid.
- PFOA and PFHxS were associated with increased odds of gout.
- PFOA, PFNA, PFOS, and PFHxS were associated with hyperuricemia among all persons.
- Exposure to perfluoroalkyls acids may be a risk factor for hyperuricemia and gout.

## Table 1

Weighted characteristics of NHANES 2009–2014 participants aged >20 years (n = 4917).

| | n | Weighted GM (SE) |
|---|---|---|
| Age (years), GM (SE) | 4917 | 44.1 (0.39) |
| Sex | | |
| Men, % (SE) | 2371 | 48.4 (0.7) |
| Women, % (SE) | 2546 | 51.6 (0.7) |
| Race/Ethnicity | | |
| Non-Hispanic White, % (SE) | 2141 | 67.8 (2.0) |
| Non-Hispanic Black, % (SE) | 1003 | 10.7 (1.0) |
| Mexican-American and Other Hispanic, % (SE) | 1190 | 14.5 (1.6) |
| Other, % (SE) | 583 | 7.0 (0.6) |
| Gout | | |
| No, % (SE) | 4717 | 96.2 (0.3) |
| Yes, % (SE) | 200 | 3.8 (0.3) |
| Hyperuricemia[a] | | |
| No, % (SE) | 3956 | 81.4 (0.8) |
| Yes, % (SE) | 961 | 18.6 (0.8) |
| Diabetes | | |
| No, % (SE) | 4079 | 86.9 (0.6) |
| Yes, % (SE) | 838 | 13.1 (0.6) |
| Hypertension | | |
| No, % (SE) | 3166 | 69.3 (0.9) |
| Yes, % (SE) | 1751 | 30.7 (0.9) |
| Chronic Kidney Disease[b] | | |
| No, % (SE) | 4103 | 87.2 (0.6) |
| Yes, % (SE) | 874 | 12.8 (0.6) |
| eGFR < 60 mL/min/1.73m$^2$, | | |
| No, % (SE) | 4514 | 94.0 (0.4) |
| Yes, % (SE) | 403 | 6.0 (0.4) |
| Albuminuria (albumin-to-creatinine ratio above 30mg/g) | | |
| No, % (SE) | 4339 | 91.5 (0.5) |
| Yes, % (SE) | 537 | 8.5 (0.5) |
| Smoking status | | |
| Current Smoker, % (SE) | 971 | 19.5 (1.0) |
| Former Smoker, % (SE) | 1156 | 23.9 (0.6) |
| Never Smoked, % (SE) | 2790 | 56.6 (0.9) |
| Education attainment | | |
| Less than High School, % (SE) | 1221 | 17.0(1.0) |
| Completed High School, % (SE) | 1047 | 20.9(1.1) |
| More than High School, % (SE) | 2649 | 62.1 (1.6) |
| Alcohol consumption | | |

| | n | Weighted GM (SE) |
|---|---|---|
| No Alcohol, % (SE) | 1625 | 26.6 (1.0) |
| 1–4 drinks per week, % (SE) | 2956 | 66.3 (1.1) |
| >4 drinks per week, % (SE) | 336 | 7.1 (0.6) |
| Uric acid (mg/dL), GM (SE) | 4917 | 5.21 (0.03) |
| BMI, GM (SE) | 4917 | 28.16 (0.13) |
| Serum Cotinine (ng/mL), GM (SE) | 4917 | 0.24 (0.03) |
| eGFR (mL/minute/1.73m$^2$), GM (SE) | 4917 | 91.47 (0.49) |
| albumin-to-creatinine ratio (mg/g) GM (SE) | 4876 | 8.15 (0.15) |
| PFOA (ng/ml), GM (SE) | 4915 | 2.37 (0.06) |
| PFNA (ng/ml), GM (SE) | 4917 | 0.92 (0.03) |
| PFDA (ng/ml), GM (SE) | 4917 | 0.23 (0.01) |
| PFHxS (ng/ml), GM (SE) | 4917 | 1.42 (0.04) |
| PFOS (ng/ml), GM (SE) | 4915 | 6.98 (0.23) |

[a] SUA levels ≥ 7 mg/dL for males and ≥6 mg/dL in females (Feig et al., 2008).

[b] eGFR < 60 mL/min/1.73 m$^2$, and/or albumin-to-creatinine ratio above 30 mg/g.

**Table 2**

Weighted Pearson correlation coefficients and related p-values analysis of log-transformed PFAAs concentrations.

| | PFOA | PFNA | PFDA | PFOS | PFHxS |
|---|---|---|---|---|---|
| PFOA | 1.00 | | | | |
| PFNA | 0.70[a] | 1.00 | | | |
| PFDA | 0.51[a] | 0.75[a] | 1.00 | | |
| PFOS | 0.67[a] | 0.74[a] | 0.65[a] | 1.00 | |
| PFHxS | 0.66[a] | 0.47[a] | 0.31[a] | 0.67[a] | 1.00 |

[a] $p < 0.00001$.

**Table 3**

Adjusted[a] beta coefficient (95% CI) for serum uric acid and adjusted[a] Odds Ratio (95% CI) for hyperuricemia and self-reported gout by single PFAA quartiles for adult participants (20 years of age and older) in NHANES 2009–2014.

| | Serum Uric Acid β (95% CI) | Hyperuricemia OR (95% CI) | Gout OR (95% CI) |
|---|---|---|---|
| PFOA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOA Q2 | 0.17 (0.06, 0.29) | 1.05 (0.77, 1.44) | 1.75 (0.90, 3.31) |
| PFOA Q3 | 0.24 (0.11, 0.37) | 1.21 (0.87, 1.69) | 2.34 (1.32, 4.15) |
| PFOA Q4 | 0.42 (0.26, 0.57) | 1.81 (1.29, 2.55) | 3.17 (1.68, 5.98) |
| p-trend | 0.0001 | 0.004 | 0.01 |
| PFNA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFNA Q2 | 0.06 (−0.05, 0.17) | 1.14 (0.83, 1.57) | 0.76 (0.37, 1.55) |
| PFNA Q3 | 0.22 (0.11, 0.32) | 1.55 (1.20, 2.01) | 1.97 (1.02, 3.78) |
| PFNA Q4 | 0.29 (0.15, 0.42) | 1.65 (1.23, 2.22) | 1.29 (0.60, 2.75) |
| p-trend | 0.0001 | 0.002 | 0.002 |
| PFDA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFDA Q2 | 0.04 (−0.07, 0.14) | 0.99 (0.73, 1.36) | 1.22 (0.75, 1.98) |
| PFDA Q3 | −0.00 (−0.12, 0.12) | 0.90 (0.64, 1.27) | 1.32 (0.70, 2.47) |
| PFDA Q4 | 0.13 (0.01, 0.25) | 1.26 (0.96, 1.67) | 1.42 (0.87, 2.32) |
| p-trend | 0.10 | 0.11 | 0.52 |
| PFOS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOS Q2 | 0.13 (0.01, 0.24) | 1.10 (0.84, 1.45) | 1.17 (0.54, 2.53) |
| PFOS Q3 | 0.21 (0.05.0.37) | 1.27 (0.92, 1.76) | 1.23 (0.56, 2.71) |
| PFOS Q4 | 0.29 (0.14, 0.44) | 1.45 (1.03, 2.03) | 1.46 (0.67, 3.16) |
| p-trend | 0.003 | 0.15 | 0.79 |
| PFHxS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFHxS Q2 | 0.14 (0.02, 0.26) | 1.15 (0.89, 1.50) | 2.35 (1.20, 4.60) |
| PFHxS Q3 | 0.22 (0.08.0.36) | 1.33 (0.95, 1.86) | 2.24 (1.15, 4.36) |
| PFHxS Q4 | 0.33 (0.19, 0.47) | 1.51 (1.12, 2.03) | 2.76 (1.36, 5.62) |
| p-trend | 0.004 | 0.06 | 0.03 |

Quartiles PFOA (ng/mL): Q1: ≤1.60; Q2: 1.61–2.47; Q3: 2.48–3.66; Q4: >3.66. Quartiles PFNA (ng/mL): Q1: ≤0.60; Q2: 0.61–0.90; Q3: 0.91–1.39; Q4: >1.39.. Quartiles PFDA (ng/mL): Q1: ≤0.12; Q2: 0.13–0.20; Q3: 0.21–0.35; Q4: >0.35. Quartiles PFHxS (ng/mL): Q1: ≤0.81; Q2: 0.82–1.49; Q3: 1.50–2.51; Q4: >2.51. Quartiles PFOS (ng/mL): Q1: >4.43; Q2: 4.44–7.33; Q3: 7.34–11.90; Q4: >11.90.

[a] Adjusted for race/ethnicity, age, sex, education attainment, alcohol consumption, self-reported cigarette smoking, serum cotinine, BMI, diabetes, hypertension, chronic kidney disease; when modeling self-reported gout as the outcome, serum uric acid was also entered as a covariate.

**Table 4**

Adjusted[a] beta coefficient (95% CI) for serum uric acid and adjusted[a] Odds Ratio (95% CI) for hyperuricemia and self-reported gout by single PFAA quartiles for adult participants (20 years of age and older) without chronic kidney disease[b] (in NHANES 2009–2014.

| | Serum Uric Acid β (95% CI) | Hyperuricemia OR (95% CI) | Gout OR (95% CI) |
|---|---|---|---|
| PFOA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOA Q2 | 0.08 (−0.03, 0.20) | 0.96 (0.64, 1.44) | 2.11 (0.72, 6.23) |
| PFOA Q3 | 0.16 (0.01, 0.31) | 1.19 (0.75, 1.88) | 2.57 (1.00, 6.59) |
| PFOA Q4 | 0.31 (0.17, 0.46) | 1.65 (1.10, 2.46) | 3.88 (1.46, 10.33) |
| p-trend | 0.001 | 0.02 | 0.05 |
| PFNA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFNA Q2 | 0.03 (−0.08, 0.15) | 1.11 (0.76, 1.62) | 1.00 (0.34, 2.97) |
| PFNA Q3 | 0.18 (0.08, 0.29) | 1.60(1.19, 2.15) | 2.75 (1.04, 7.32) |
| PFNA Q4 | 0.24 (0.11, 0.37) | 1.72 (1.23, 2.41) | 1.86 (0.66, 5.26) |
| p-trend | 0.0002 | 0.002 | 0.02 |
| PFDA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFDA Q2 | 0.00 (−0.09, 0.10) | 0.94 (0.66, 1.34) | 1.56 (0.79, 3.09) |
| PFDA Q3 | −0.05 (−0.17, 0.07) | 0.86 (0.57, 1.25) | 1.42 (0.64, 3.14) |
| PFDA Q4 | 0.12 (0.00, 0.24) | 1.30 (0.94, 1.80) | 1.98 (1.06, 3.67) |
| p-trend | 0.09 | 0.11 | 0.18 |
| PFOS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOS Q2 | 0.03 (−0.10, 0.15) | 0.94 (0.68, 1.30) | 1.73 (0.60, 4.94) |
| PFOS Q3 | 0.13 (−0.02, 0.28) | 1.26 (0.89, 1.79) | 1.56 (0.51, 4.78) |
| PFOS Q4 | 0.20 (0.06, 0.34) | 1.35 (0.92, 1.99) | 1.93 (0.71, 5.22) |
| p-trend | 0.02 | 0.19 | 0.58 |
| PFHxS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFHxS Q2 | 0.07 (−0.07, 0.20) | 1.17 (0.82, 1.68) | 3.81 (1.40, 10.38) |
| PFHxS Q3 | 0.13 (0.00, 0.26) | 1.34 (0.86, 2.07) | 3.10(1.14, 8.44) |
| PFHxS Q4 | 0.22 (0.08, 0.36) | 1.40 (0.94, 2.07) | 3.90 (1.33, 11.49) |
| p-trend | 0.02 | 0.39 | 0.06 |

Quartiles PFOA (ng/mL): Q1: ≤1.60; Q2: 1.61–2.47; Q3: 2.48–3.66; Q4: >3.66. Quartiles PFNA (ng/mL): Q1: ≤0.60; Q2: 0.61–0.90; Q3: 0.91–1.39; Q4: >1.39. . Quartiles PFDA (ng/mL): Q1: ≤0.12; Q2: 0.13–0.20; Q3: 0.21–0.35; Q4: >0.35, Quartiles PFHxS (ng/mL): Q1: ≤0.81; Q2: 0.82–1.49; Q3: 1.50–2.51; Q4: >2.51. Quartiles PFOS (ng/mL): Q1: ≤4.43; Q2: 4.44–7.33; Q3: 7.34–11.90; Q4: >11.90.

[a] Adjusted for race/ethnicity, age, sex, education attainment, alcohol consumption, self-reported cigarette smoking, serum cotinine, BMI, diabetes, hypertension, and eGRF; when modeling self-reported gout as the outcome, serum uric acid was also entered as a covariate.

[b] Chronic kidney diseases defined as eGFR ≥60 mL/min/1.73 $m^2$ and/or albuminuria (>30. mg/g).

**Table 5**

Adjusted[a] beta coefficient (95% CI) for serum uric acid and adjusted[a] Odds Ratio (95% CI) for hyperuricemia and self-reported gout by single PFAA quartiles for adult participants (20 years of age and older) with chronic kidney disease[b] (in NHANES 2009–2014.

| | Serum Uric Acid β (95% CI) | Hyperuricemia OR (95% CI) | Gout OR (95% CI) |
|---|---|---|---|
| PFOA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOA Q2 | 0.14 (−0.38 0.65) | 1.15 (0.69, 1.92) | 1.83 (0.79, 4.19) |
| PFOA Q3 | −0.05 (−0.63, 0.53) | 0.95 (0.53, 1.69) | 3.02 (1.28, 7.15) |
| PFOA Q4 | 0.60 (−0.04, 1.24) | 1.82 (0.96, 3.47) | 2.73 (1.28, 5.84) |
| p-trend | 0.02 | 0.21 | 0.04 |
| PFNA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFNA Q2 | 0.29 (−0.10, 0.68) | 1.40 (0.82, 2.39) | 0.65 (0.27, 1.54) |
| PFNA Q3 | 0.31 (0.01, 0.61) | 1.41 (0.87, 2.30) | 1.43 (0.74, 2.75) |
| PFNA Q4 | 0.47 (0.14, 0.80) | 1.36 (0.78, 2.36) | 0.86 (0.44, 1.69) |
| p-trend | 0.04 | 0.47 | 0.21 |
| PFDA Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFDA Q2 | 0.34 (−0.03, 0.72) | 1.32 (0.66, 2.65) | 1.09 (0.52, 2.29) |
| PFDA Q3 | 0.19 (−0.13, 0.52) | 0.98 (0.60, 1.61) | 1.62 (0.79, 3.31) |
| PFDA Q4 | 0.26 (−0.09, 0.61) | 1.26 (0.64, 2.46) | 0.77 (0.35, 1.70) |
| p-trend | 0.34 | 0.73 | 0.41 |
| PFOS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFOS Q2 | 0.60 (0.15, 1.05) | 1.93 (0.91, 4.06) | 0.88 (0.26, 2.92) |
| PFOS Q3 | 0.31 (−0.02, 0.70) | 0.85 (0.40, 1.77) | 1.08 (0.38, 3.07) |
| PFOS Q4 | 0.38 (0.06, 0.83) | 1.15 (0.53, 2.50) | 1.08 (0.39, 2.94) |
| p-trend | 0.08 | 0.12 | 0.97 |
| PFHxS Q1 | 0 (Referent) | 1 (Referent) | 1 (Referent) |
| PFHxS Q2 | 0.40 (−0.03, 0.84) | 0.91 (0.49, 1.70) | 1.53 (0.57, 4.05) |
| PFHxS Q3 | 0.33 (−0.02, 0.67) | 0.87 (0.49, 1.53) | 1.85 (0.76, 4.52) |
| PFHxS Q4 | 0.42 (0.06, 0.78) | 1.28 (0.52 2.64) | 2.31 (0.96, 5.57) |
| p-trend | 0.12 | 0.49 | 0.31 |

Quartiles PFOA (ng/mL): Q1: ≤1.60; Q2: 1.61–2.47; Q3: 2.48–3.66; Q4: >3.66. Quartiles PFNA (ng/mL): Q1: ≤0.60; Q2: 0.61–0.90; Q3: 0.91 – 1.39; Q4: >1.39. . Quartiles PFDA (ng/mL): Q1: >0.12; Q2: 0.13–0.20; Q3: 0.21–0.35; Q4: >0.35, Quartiles PFHxS (ng/mL): Q1: ≤0.81; Q2: 0.82–1.49; Q3: 1.50–2.51; Q4: >2.51. Quartiles PFOS (ng/mL): Q1: ≤4.43; Q2: 4.44–7.33; Q3: 7.34–11.90; Q4: >11.90.

[a] Adjusted for race/ethnicity, age, sex, education attainment, alcohol consumption, self-reported cigarette smoking, serum cotinine, BMI, diabetes, hypertension, and eGRF; when modeling self-reported gout as the outcome, serum uric acid was also entered as a covariate.

[b] Chronic kidney diseases defined as eGFR ≥60 mL/min/1.73 $m^2$ and/or albuminuria (>30. mg/g).