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Perfluoroalkyls/polyfluoroalkyl substances and dental caries experience in children, ages 3–11 years, National Health and Nutrition Examination Survey, 2013–2014

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Abstract

Objective: The objective of this research is to determine the association of seven perfluoroalkyl and polyfluoroalkyl substances versus dental caries experience in US children, ages 3–11 years.

Methods: A cross-sectional study design was used in the analysis of National Health and Nutrition Examination Survey 2013–2014 serological data of perfluoroalkyl and polyfluoroalkyl substances. The seven perfluoroalkyl and polyfluoroalkyl substances were: 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; perfluorodecanoic acid; perfluorononanoic acid; perfluorohexane sulfonic acid; linear isomers of perfluorooctanoate; linear perfluorooctane sulfonate; and monomethyl branched isomers of perfluorooctane sulfonate. Two summative variables were created: monomethyl branch isomers of perfluorooctane sulfonic acid with linear isomer of perfluorooctane and branch isomers of perfluorooctanoate with linear isomer perfluorooctonate.

Results: In unadjusted logistic regression, in which the comparison was between the less than 75th percentile reference group and the 75th and above percentile group, higher perfluorodecanoic acid was associated with dental caries experience [unadjusted odds ratio: 1.79 (95% CI: 1.19, 2.46; $P = 0.0069$); adjusted odds ratio: 1.54 (95% CI: 1.03, 2.30; $P = 0.0385$)].

Conclusions: Of the seven examined perfluoroalkyl and polyfluoroalkyl substances, only perfluorodecanoic acid had an association with dental caries experience in an unadjusted model and adjusted logistic regression model.

Keywords

perfluorinated compounds; perfluoroalkyl; polyfluoroalkyl; C8; PFOS; PFOA

Introduction

Perfluoroalkyl and polyfluoroalkyl substances are ubiquitous, man-made chemicals with strong, stable carbon-fluoride bonds in their perfluoroalkyl moiety ($C_nF_{2n+1}^-$).[1] They are

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used in water-resistant and soil-resistant items (carpeting, flooring, textiles, food contact paper, cardboard, or packaging used to prevent seepage, nonstick cookware, and so on) electronics, surfactants, lubricants, and paints. The substances are persistent in the environment.[2,3] Human exposure to perfluoroalkyl or polyfluoroalkyl substances occurs by ingestion of contaminated food and/or water, occupational exposure, breathing contaminated air, dermal exposure, or hand-to-mouth exposure.[4]

Laboratory animal studies have provided much of the information about perfluoroalkyls and polyfluoroalkyl substances. From these studies, researchers identified adverse effects of perfluoroalkyl and polyfluoroalkyl substances as altered liver function (hepatomegaly, hepatic peroxisome proliferation), reduced testosterone production, changes in the thyroid stimulating hormone (TSH) and thyroxine levels, reduced birth weight, delayed growth and development, increases in pregnancy loss, neonatal mortality, altered inflammatory responses, and altered cytokine expression.[4–6] For example, in 2002 and 2009, researchers Yang *et al.*[7] and Guruge *et al.*[8] found that there was suppression of an adaptive immune response and natural killer cell activity in mice exposed to perfluorooctanoate.

A variety of *in vitro* studies on perfluoroalkyl and polyfluoroalkyl substances have been conducted to gain an understanding of the toxic properties, effects, and modes of action of perfluoroalkyl and polyfluoroalkyl substances.[9] Rainieri *et al.* (2007) found that 24 hours after being exposed to perfluorononanoic acid, macrophage cells (TLT cells) showed great cytotoxity and apoptosis induced by oxidative stress. Researchers examining healthy primary human CD4+ T cells showed that perfluorooctane sulfonate suppressed interleukin-2 production in doses within the high end of human exposure.[10]

In human studies, dietary intake of food contaminated with perfluoroalkyl and polyfluoroalkyl substances is the major exposure route.[11] Perfluoroalkyl and polyfluoroalkyl substances can penetrate the placental barrier for fetal exposure.[12] Prenatal exposure has been associated with adverse birth outcomes, allergic responses, and cancer.[12,13] In the C8 Health Project conducted near Parkersburg, West Virginia, epidemiologists examined exposures in 69,030 adults. Researchers reported probable associations of perfluorooctanoate (C8) with hypercholesteremia, ulcerative colitis, thyroid dysfunction, testicular cancer, kidney cancer, preeclampsia, and elevated blood pressure during pregnancy.[4]

Mixed results in health outcomes occurred when researchers studied children. In Project Viva (Boston), researchers reported that early life exposure to perfluoroalkyl substances did not have an adverse effect on metabolic function, and actually had the effect of lowering insulin resistance.[14] In another study, the Spanish INMA birth cohort study, no significant evidence of links of cardiometabolic risk and perfluoroalkyl substances were found in children.[15] Conversely, prenatal exposure to perfluorooctonate, perfluorodecanoic acid, perfluorododecanoic acid, or perfluorohexane sulfonic acid was related to an increase in childhood atopic dermatitis (a disease associated with immune dysfunction) in females.[16] Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances was associated with greater adiposity at age 8 years and a rapid increase in body mass index at ages 2–8 years in

the prospective cohort Health Outcomes and Measures of the Environment study conducted in Cincinnati, Ohio.[17]

Research in humans is limited, inconsistent, and controversial. Perfluoroalkyl and polyfluoroalkyl substances have been found in blood, liver, urine, hair, cord blood, and nails and bioaccumulate in those tissues.[18] The chemicals were reported to be toxic and carcinogenic for liver tissue, and may interfere with the immune system and the endocrine system.[18] Their toxicity mechanism is currently unclear[18] and the public health impact is currently unknown.[19–21] In children, the research is even more challenging. In addition to determining exposure levels, researchers must also consider a) other factors known to influence health; b) potential confounders; and c) the effects of childhood periods of development in which exposure could have differing effects on health.[22]

Dental caries experience and perfluoroalkyl and polyfluoroalkyl substances

Dental caries is a complex disease involving many factors beyond the microbiome, dietary carbohydrates, plaque, brushing/flossing, and salivary output/buffering capacity/pH. Dental caries is related to several chronic conditions, and many of those conditions are associated with perfluoroalkyl and polyfluoroalkyl substances. Therefore, it is possible that dental caries itself is associated with perfluoroalkyl and polyfluoroalkyl substances.[23] Several mechanisms of action have been postulated. Perfluoroalkyls and polyfluoroalkyl substances were associated with decreases in spinal bone mineral density in premenopausal women.[24] As bone and dentin are similar in composition and structure, tooth mineralization could be affected by perfluoroalkyls and polyfluoroalkyl substances as bone mineral density is in premenopausal women.[25] In addition, the perfluoroalkyls and polyfluoroalkyl substances affect TSH. Thyroid hormones influence tooth maturation. Low TSH is associated with enamel hypoplasia; therefore, perfluoroalkyl and polyfluoroalkyl substances could have the same effect through lowering TSH.

Other environmental factors (lead[26] and tobacco smoke[27]) have been shown to be contributing factors in dental caries. The pathways of their effects may be like the effect of perfluoroalkyl and polyfluoroalkyl substances upon developing teeth. In addition, changes in a developing, immature immune system by these chemicals and the effect on saliva could result in physiologic changes on the vulnerability of teeth.[27]

Another plausible mechanism is that perfluoroalkyl and polyfluoroalkyl substances, which are suspected estrogen disruptors,[28–32] disrupt estrogen in its role to upregulate carbonic anhydrase, an enzyme needed to properly build apatite enamel crystals.[32] A change in crystal structure could increase the vulnerability of teeth for dental caries.

It is important to know if perfluoroalkyl and polyfluoroalkyl substances do affect tooth vulnerability to caries, particularly in early childhood. The purpose of this research is to determine the association of various perfluoroalky and polyfluoroalkyl substances with dental caries experience in children ages 3 years to 11 years.

Methods

Ethical statement

The West Virginia University Institutional Review Board has acknowledged this study as non-human subject research (Protocol number: 1806164862).

Study design

A cross-sectional research design was used for this study.

Data source

The data used for this study are from the National Health and Nutrition Examination Survey (NHANES) for the years 2013–2014. The data are publicly available from the NHANES website at https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013. The NHANES is a survey of the National Health Center for Health Statistics at the Centers for Disease Control and Prevention on noninstitutionalized US population.

Study participants

Approximately one-third of the children, ages 3–11 years (n = 639), had serological specimens analyzed for perfluoroalkyl and polyfluoroalkyl substances in the NHANES 2013–2014. These children were included in the present study.

Description of procedures for variables of interest conducted in NHANES 2013–2014

NHANES scientists completed solid phase extraction of sera. The samples were coupled to high-performance liquid chromatography-turbo ion spray ionization-tandem mass spectrometry to determine 14 perfluoroalkyls and polyfluoroalkyl substances (Table 1).[33] The scientists diluted samples with formic acid and injected 50 μL of each sample into a column switching system.[33] The analytes were separated by chromatography and quantified with tandem mass spectrometry.[33] If a perfluoroalkyl or polyfluoroalkyl substance value was below the limit of detection, NHANES scientists imputed a value equal to the lower limit of detection divided by the square root of 2.[33] The tests are extremely adequate as they have a lower limit of detection of 0.1 ng/ml.

Dental caries experience (any current dental caries and any dental restorations) in the NHANES was determined by calibrated US licensed dentists who had annual retraining, and were visited by the reference examiner up to three times per year to replicate 20–25 examinations.[34] The dentists used a #5 reflecting mirror and a #23 dental explorer in identifying dental caries and dental restorations. The 1968 Radike criteria for coronal caries was used (a modified DMFS index).[35]

NHANES scientists ascertained fluoride water concentrations by testing water samples from participants' households. The fluoride concentration was determined electrometrically with an ion-specific electrode having a limit of detection of 0.019 mg/l.[34]

Perfluoroalkyl and polyfluoroalkyl substances used in this study

Of the 14 perfluoroalkyl and polyfluoroalkyl substances analyzed by NHANES scientists, 7 were used in this study as the others had sample sizes at or below the lower limit of detection, which were too low for meaningful analyses[36] (Table 1). In addition, two summative concentrations were used. The values of the monomethyl branch isomers of perfluorooctane sulfonic acid and linear isomer of perfluorooctane sulfonate were added to create the sum of perfluorooctane sulfonic acid isomers (PPFOS), and the values of the branch isomers of perfluorooctanoate and linear isomer perfluorooctonate were added to create the sum of perfluooctanoate isomers (PPFOA).

Dental variable used in this study

The variable, dental caries experience, was created from clinically observed current dental caries and/or dental restoration (yes, no), as described above.

Other variables used in this study

Other available variables known to be associated with dental caries were also included in this study. These were: age (≥3 to ≤5 years, >5 to ≤11 years); sex (female, male); race/ethnicity (Non-Hispanic white, Non-Hispanic black, Mexican American, other); tooth brushing frequency (once or less daily, twice or more daily); dental visit (within the previous year, more than 1 year or never); insurance status (yes, no); ratio of family income to poverty level guidelines (<2.00, 2 and above, missing; based upon the Department of Health and Human Services Poverty Guidelines),[37] and fluoride in the child's water (a continuous variable). Body mass index for children (underweight/normal weight, overweight/obese based upon CDC percentages) was also included (Figure 1).

Statistical analysis

Statistical analyses were conducted with SAS version 9.4 (Cary, NC). Specific survey weights to analyze the perfluoroalkyl and polyfluoroalkyl substances (variable WTSS2YR in the SSPFAC_H NHANES dataset) and masked variance pseudoprimary sampling unit and masked variance pseudostratum were included to account for the NHANES survey design. An *a priori* level of significance was set at <0.05.

Data analyses included frequency determinations and weighted percentages of sample characteristics of the perfluoroalkyl and polyfluoroalkyl substances and bivariate (Rao-Scott Chi- square) evaluation of dental caries experience versus the variables. Geometric means of the perfluoroalkyl and polyfluoroalkyl substances were used as the data are skewed, whereas the arithmetic mean is sensitive to outliers (and would therefore not be a good summative statistic to use), the median is not, and, therefore, the geometric mean is more appropriate.[38] It was calculated as:

$$\text{Geometric mean} = \text{exponentiation}\left[(\log(x_1) + \log(x_2) + \ | \cdots \log(x_n)/n\right].$$

Odds ratios and adjusted odds ratios were determined with logistic regression analyses. The adjusted model included epidemiological considerations as well as the results from the

bivariate analyses in which variables failing to reach an *a priori* level of significance (<0.05) were excluded. The adjusted models included the specific perfluoroalkyl or polyfluoroalkyl substance, age, sex (which failed to reach significance in the bivariate analysis, but was included for epidemiological considerations), race/ethnicity, ratio of family-income-to-poverty-level guidelines, dental visit, tooth brushing frequency, and fluoride in the water. Percent of sugar in the diet, although an epidemiological factor, was not included due to the number of missing data points and the >90% to 10% split of the data for recommended sugar intake (see Table 2).

Results

There were 629 children, aged ≥3 to ≤11 years, whose data were used as the sample for this current study. The sample was 51.0% male; 51.5% Non-Hispanic white; 50.2% having a ratio of family-income-to-poverty level of less than 2.0;68.0% under or normal weight; 67.6% ages greater than 5–11 years; 95.1% with insurance, and 46.2% having had caries experience (Table 2). The highest geometric mean for a single perfluoroalkyl or polyfluoroalkyl substance was for perfluorooctane sulfonate with monoethyl branch isomers of perfluorooctane sulfonic acid. Its geometric mean and 95% confidence interval (95% CI) was 2.51 (95%CI: 2.30, 2.74) ng/ml. When the monomethyl branch isomers of perfluorooctane sulfonic acid were added, the summative perfluorooctane sulfonic acid geometric mean was 3.88 (95%CI: 3.53, 4.27) ng/ml (Table 2).

In bivariate, Chi-square analyses (Table 3), perfluorodecanoic acid was the only perfluoroalkyl or polyfluoroalkyl substance statistically significantly associated with dental caries experience ($P = 0.0002$). Older age ($P = 0.0178$), Mexican-American ethnicity ($P = 0.0051$), low-family-income-to-poverty ratio ($P = 0.0039$), and less tooth brushing frequency ($P = 0.0005$) having a dental visit within the year were also independently associated with dental caries experience in the bivariate analyses. Body mass index for children, insurance status, sugar in diet, and sex failed to reach significance with dental caries experience.

In unadjusted logistic regression analyses in which the comparison was between the less than 75th percentile reference group and the 75th percentile and above group, higher perfluorodecanoic acid was associated with dental caries in an unadjusted model [odds ratio (UOR) 1.79 (95%CI: 1.19, 2.46; $P = 0.0069$)] and in an adjusted model [adjusted odds ratio (AOR) 1.54 (95%CI: 1.03, 2.30; $P = 0.0385$)] (Table 4). Other perfluoroalkyl and polyfluoroalkyl substances failed to reach significance in logistic regression analyses.

When logistic regression analyses were stratified by sex, the female analyses involved the data of 291 children and the male analyses involved the data of 338 children. For females, in the unadjusted logistic regression in which the comparison was between the less than 75th percentile reference group and the 75th percentile and above group for perfluorodecanoic acid, the UOR was 1.52 (95%CI: 0.75, 3.07, $P = 0.2282$), and it was 1.55 (95%CI: 0.85, 2.83; $P = 0.1433$) for the adjusted analysis.

For males, in the unadjusted logistic regression analysis in which the comparison was between the less than 75th percentile reference group and the 75th percentile and above

group for perfluorodecanoic acid, the UOR was 1.95 (95%CI: 1.33, 2.86; $P = 0.0020$). The association remained positive for the 75th percentile and above group with an adjusted OR of 1.63 (95%CI: 0.96, 2.76; $P = 0.0661$); however, it was no longer statistically significant.

When logistic regression analyses were stratified by age, the data were from 178 children, ages 3 to and including 5 years in the younger analyses, and the data were from 461 children, ages 5 years to and including 11 years in the older analyses. For the younger group, in unadjusted logistic regression analysis in which the comparison was between the less than 75th percentile reference group and the 75th percentile and above group for perfluorodecanoic acid, the UOR was 1.84 (95%CI: 0.81, 4.17 $P = 0.1332$) and 1.64 (95%CI: 0.66, 4.05; $P = 0.2627$) for the adjusted analysis.

For the older children, in the unadjusted logistic regression analyses in which the comparison was between the less than 75th percentile reference group and the 75th percentile and above group for perfluorodecanoic acid, the UOR was 1.64 (95%CI: 1.21, 2.24; $P = 0.0036$). The association remained positive for the 75th percentile and above group with an adjusted OR of 1.52 (95%CI: 0.99, 2.33; $P = 0.0541$); however, it was no longer statistically significant.

Several other factors previously identified as being associated with dental caries were significant factors in the logistic regression analysis in this study. Age was significantly associated with dental caries [>5 to ≤11 years as compared with younger children, UOR = 1.85 (95%CI: 1.07, 3.21; $P = 0.0307$); AOR =2.07 (95%CI: 1.17, 3.67; $P = 0.0163$)]. Mexican American status as compared with non-Hispanic white was associated with dental caries [UOR =1.99 (95%CI: 1.26, 3.13; $P = 0.0059$); AOR = 1.85 (95%CI: 1.13, 3.05; $P = 0.0185$)]. Having a federal poverty index less than 2.0 as compared with higher indices was significantly associated with dental caries [UOR = 1.76 (95%CI: 1.11, 2.80; $P = 0.0197$); AOR = 1.89 (95%CI: 1.27, 2.81; $P = 0.0039$)]. Brushing once or fewer times a day as compared with brushing more frequently was associated with dental caries [UOR = 1.52 (95%CI: 1.14, 2.02; $P = 0.0071$); AOR = 1.78 (95%CI: 1.23, 2.59; $P = 0.0049$)]. Having a dental visit within the previous year as compared with having a dental visit over a year ago was associated with a less likelihood of dental caries [UOR = 0.46 (95% CI: 0.22, 0.96; $P = 0.0409$)]. Higher fluoride in water content was also related to a less likelihood of dental caries [unadjusted beta = 0.54 (95%CI: 0.32, 0.92, $P = 0.0271$); adjusted = 0.47 (95% CI: 0.25, 0.87; $P = 0.0189$)].

Discussion

In this study of the association of dental caries experience and perfluoroalkyl and polyfluoroalkyl substances, perfluorodecanoic acid was significantly associated with dental caries experience in the unadjusted and adjusted logistic regression models. The observed values of each of the perfluoroalkyl and polyfluoroalkyl substances in this study were consistent with previous research specific to this age group[36] and similar to those reported by the CDC.[39] It should be noted that over half of the children in the study had levels of perfluorodecanoic acid below detection. This indicates a potential trend of decreased perfluorodecanoic acid exposure for children ages 3–11 years. As perfluorodecanoic acid is

a large, stable perfluoroalkyl with associated adverse health effects, having a trend of fewer exposures is a public health benefit.[36]

Perfluoroalkyl and polyfluoroalkyl substances do not occur naturally; however, they are very persistence in the environment.[40] Although they are no longer produced in the United States, there is much attention focused on their potential health impacts.[40] There is an increased concern of the potential for health effects occurring *at much lower levels* than previously suspected. The most troubling perfluoroalkyl and polyfluoroalkyl substances are the large ones (with at least six carbon atoms) as they are the most stable and persistent.[40]

Epidemiological studies involving children and perfluoroalkyl and polyfluoroalkyl substances

As previously noted, there are few studies of perfluoroalkyl and polyfluoroalkyl substances involving the health of children. Food and water contamination are the two primary routes of human exposure to perlfuoroalkyl and polyfluoroalkyl substances, followed by dust inhalation and dust ingestion.[41–43] There have been biomonitoring studies that have been performed in which the researchers indicated an association between the consumption of contaminated drinking water and high concentrations of perfluoroalkyl and polyfluoroalkyl substances in blood plasma and prenatal maternal cord blood.[11,13]

The attention to the presence of perfluoroalkyl and polyfluoroalkyl substances in water and air has led to several regulatory actions to limit such exposures in humans.[2] Specific to this study and specific to perfluorodecanoic acid, researchers from the Agency for Toxic Substances and Disease Registry (an agency in the Department of Health and Human Services) indicated that there are insufficient data to determine the acute, intermediate, and chronic duration inhalation for the minimal risk level of exposure to perfluorodecanoic acid.[40] Most of the research involving perfluorodecanoic acid has been limited to animal studies.[40]

Perfluorodecanoic acid may have several pathways to influence tooth growth and development. Though tooth growth and development have not been specifically studied with perfluorodecanoic acid, its effects on other cells may be similar to its effects on tooth growth and development. It activates peroxisome proliferator-activated receptor alpha and initiates oxidative stress in the metabolism of lipids, glucose, and amino acids.[3] It promotes cell proliferation through a hypothesized change in gene expression in the vascular endothelial growth factor signaling pathway for gastric cells.[44] Perfluorodecanoic acid was found to bind to and alter the structure of two hemoproteins— bovine hemoglobin and myoglobin indicating the potential of perfluorodecanoic acid to alter protein structures in general.[45] In addition, as an estrogen disruptor,[28–31] perfluorodecanoic acid may disrupt carbonic anhydrase, needed for sound enamel development.[32]

Although not a focus of this study, the typically accepted predictors of dental caries experience were significantly associated with dental caries for the participants. Dental caries was associated with brushing less than twice a day ($P = 0.0049$) as compared with brushing two or more times a day; no dental visits within the previous year ($P = 0.0195$) as compared with having a dental visit within the year; ages >5 to ≤11 ($P = 0.0163$) as compared with

children ages 3–5; <2.0 ratio of family-income-to-poverty ($P = 0.0039$) as compared with higher income-to-poverty ratios; and non-Hispanic Black race/ethnicity ($P = 0.0185$) as compared with non-Hispanic White race/ethnicity.

Strengths and limitations

This study is limited by sample size. A larger sample size would have been desirable for an increase in power. However, only NHANES 2013–2014 had perfluoroalkyl and polyfluoralkyl substance data for children ages 3–11; the data were not available for additional years at this time. In addition, only a one-third subset of the children ages 3–11 years who were participants in 2013–2014 provided samples to be tested. Other factors that would have been helpful in this research were not available in the NHANES data source, or could not be included in the research due to the limitations imposed by the sample size/degrees of freedom/missing data. The data are cross sectional; therefore, the period of development in which the children were exposed and the degree to which an impact could have occurred were not available.

Nevertheless, the research was conducted with data from the National Health and Nutrition Examination Survey, which is a highly regarded national study in the United States with rigorous criteria and laboratory protocols. Data sample weights, masked variance pseudoprimary sampling unit, and the masked variance pseudostratum were used to adjust for the complex study design, and many known factors associated with dental caries experience were included in the analyses.

Conclusion

This is the first study, to the authors' knowledge of the relationship of perfluoroalkyl and polyfluoroalkyl substances and dental caries experience in young children. Of the seven examined substances, only perfluorodecanoic acid was associated with dental caries experience in unadjusted and unadjusted logistic regression analyses. The results also support associations of greater likelihood of dental caries with older age, lower income, and Mexican American status (as compared with non-Hispanic white); and with the lesser likelihood of dental caries with brushing more than once a day, having a dental visit within a year (as compared with over a year), and water fluoridation.

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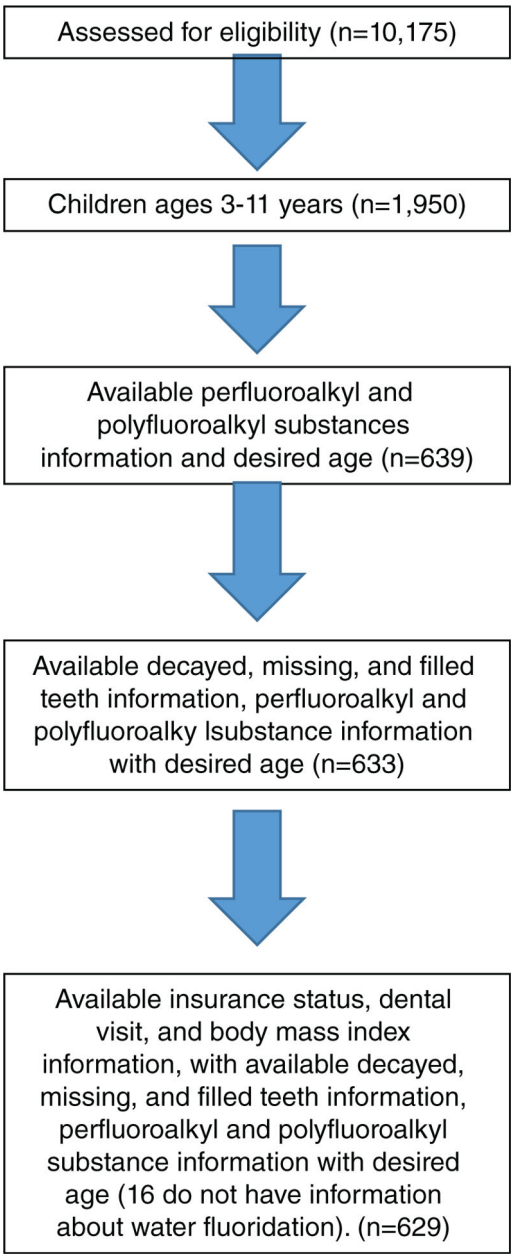

Figure 1.
Eligible sample, US children ages 3–11 years, National Health and Nutrition Examination Survey, 2013–2014.

Table 1

Perfluoroalkyl and Polyfluoroalkyls Substances Analyzed in US Children, Ages 3–11 Years, National Health and Nutrition Examination Survey, 2013–2014

	Abbreviation	Molecular formula	g/mol
1. Perfluorooctane sulfonamide	PFSA	$C_8H_2F_{17}NO_2S$	499.14
2. 2-(N-methyl-perfluorooctane sulfonamide) acetic acid[§]	**MPAH**	$C_{11}H_6F_{17}NO_4S$	571.205
3. 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid	EPAH	$C_{12}H_8F_{17}NO_4S$	585.232
4. Perfluorodecanoic acid[§]	**PFDA**	$C_{10}HF_{19}O_2$	514.086
5. Perfluorobutane sulfonic acid	PFBS	$C_6HF_{13}O_3S$	400.11
6. Perfluoroheptanoic acid	PFHP	$C_7HF_{13}O_2$	364.062
7. Perfluorononanoic acid[§]	**PFNA**	$C_9HF_{17}O_2$	464.078
8. Perfluoroundecanoic acid	PFUA	$C_{11}HF_{21}O_2$	564.093
9. Perfluordodecanoic acid	PFDO	$C_{12}HF_{23}O_2$	614.101
10. Perfluorohexane sulfonic acid[§]	**PFHxS**	$C_6HF_{13}O_3S$	400.11
11. Linear isomers of perfluorooctanoate[§]	**NPFOA**	$C_8F_{15}NaO_2$[*]	436.052
12. Branched isomers of perfluorooctanoate	BPFOA[†]		
13. Linear perfluorooctane sulfonate[§]	**NPFOS**	$C_8HF_{17}O_3S$	500.126
14. Monomethyl branched isomers of perfluorooctane sulfonate[§]	**MPFOS**[‡]		

[*] Sodium salt of the perfluoroocanate.

[†] Branched isomers include perfluoro-3-methylheptanoic acid, perfluoro-4-methyheptanoic acid, perfluoro-5-methyheptanoic acid, perfluoro-6-methyheptanoic acid, perfluoro-4,4-dimethylhexanoic acid, perfluoro-5,5-dimethylhexanoic acid, perfluoro-3,5-dimethylhexanoic acid, and perfluoro-4,5-dimethylhexanoic acid.[28]

[‡] Monomethyl branched isomers of perfluorooctane sulfonate include perfluoro-3-methylheptane sulfonate, perfluoro-4-methylheptane sulfonate, perfluoro-5-methylheptane sulfonate, and perfluoro-6-methylheptane sulfonate.[28]

[§] These perfluoroalkyl/polyfluoroalkyl substances were used in the study, and the other substances had sample sizes at or above the lower limit of detection that were too low for meaningful analyses.[46]

Bold items have P-values <.05.

Table 2

Sample Characteristics, National Health and Nutrition Examination Survey, 2013–2014

	***N* (weighted %)**
Total Sample	629 (100%)
Age in years	
≥3 to ≤5	178 (32.4%)
>5 to <11	451 (67.6%)
Sex	
Female	291 (49.0%)
Male	338 (51.0%)
Race/ethnicity	
Non-Hispanic white	163 (51.5%)
Non-Hispanic black	159 (13.9%)
Mexican American	215 (24.7%)
Other	92 (9.8%)
Ratio of family income to poverty guidelines	
<2.00	391 (50.2%)
2.00 and above	206 (45.7%)
Missing	32 (4.1%)
Body mass index for children *	
Underweight/normal weight	404 (68.0%)
Overweight/obese	225 (32.0%)
Insurance	
Yes	597 (95.1%)
No	32 (4.9%)
Dental caries experience	
Yes	321 (46.2%)
No	308 (53.8%)
Tooth brushing frequency	
≤1 time per day	209 (35.6%)
≥2 times per day	420 (64.4%)

	N (weighted %)		
Dental visit			
Within the previous year	540 (86.9%)		
>1 year or no previous care	89 (13.1%)		
Fluoridated water as a continuous variable			
Mean (95% CI) mg/l, SE	0.54 (0.44, 0.64), 0.05		
(16 with missing data)			
Percent of sugar in diet			
<10%	22	3.0%	
≥10%	495	80.5%	
Missing	112	16.5%	
2(N-methyl-perfluoro sulfon amide acetic) acid			Values 0.07[†]–6.75 ng/ml
Geometric mean not calculated[≠]			
Number less than limit of detection	331	46.7	<0.10 ng/ml
Detection to 75th percentile	160	27.0	≥0.1 to <0.26 ng/ml
75th—100th percentile	138	26.2	≥0.26
Perfluorodecanoic acid			Values 0.07[†]–2 ng/ml
Geometric mean not calculated[≠]			
Number less than limit of detection	332 (52.2%)		<0.10 ng/ml
Detection to 75th percentile	118 (21.1%)		≥0.10 to <0.17 ng/ml
75th—100th percentile	179 (26.6%)		≥0.17 ng/ml
Perfluornononanoic acid			Values 0.07[†]–52.92 ng/ml
Geometric mean [95% Confidence Level]			0.79 [0.68, 0.93] ng/ml
Up to 25th percentile	160 (24.5%)		<0.50 ng/ml
25th-50th percentile	149 (24.6%)		≥0.50 to <0.70 ng/ml
50th-75th percentile	153 (25.7%)		≥0.70 to <1.07 ng/ml
75th—100th percentile	167 (25.2%)		≥1.07 ng/ml
Perfluorohexane sulfonic acid			Values 0.07[†]–12.9 ng/ml
Geometric mean [95% Confidence level]			0.84 [0.76, 0.94] ng/ml
Up to 25th percentile	167 (23.8%)		<0.50 ng/ml

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	N (weighted %)	
25th to 50th percentile	182 (25.2%)	≥0.50 to <0.81 ng/ml
50th to 75Th percentile	130 (25.1%)	≥0.81 to <1.24 ng/ml
75th to 100th percentile	150 (25.8%)	≥1.24 ng/ml
Linear isomer of perfluorooctanoate		Values 0.07[†]–8.22 ng/ml
Geometric mean [95% Confidence level]		1.81 [1.64, 2.01] ng/ml
Up to 25th percentile	184 (24.4%)	<1.31 ng/ml
25th to 50th percentile	171 (25.1%)	≥1.31 to <1.82 ng/ml
50th to 75th percentile	150 (25.2%)	≥1.82 to <2.51 ng/ml
75th to 100th percentile	124 (25.2%)	≥2.51 ng/ml
Linear isomer of perfluorooctane sulfonate		Values 0.5–26.54 ng/ml
Geometric mean [95% confidence level]		2.51 [2.30, 2.74] ng/ml
Up to 25th percentile	157 (24.2%)	<1.67 ng/ml
25th-50th percentile	164 (25.3%)	≥1.67 to <2.47 ng/ml
50th-75th percentile	154 (25.3%)	≥2.47 to <3.56 ng/ml
75th—100th percentile	154 (25.1%)	≥3.56 ng/ml
Monomethyl branch isomers of perfluorooctanesulfonic acid		Values 0.18–10.68 ng/ml
Geometric mean [95% confidence level]		1.23 [1.09, 1.40] ng/ml
Up to 25th percentile	171 (25.0%)	<0.77 ng/ml
25th-50th percentile	173 (24.6%)	≥0.77 to 1.27 ng/ml
50th-75th percentile	138 (25.1%)	≥ 1.27 to 1.89 ng/ml
75th—100th percentile	147 (25.2%)	≥1.89 ng/ml
(ΣPFOS) Monomethyl branch isomers of perfluorooctanesulfonic acid and linear isomer of perfluorooctane sulfonate		Values 0.18–26.54 ng/ml
Geometric mean [95% confidence level]		3.88 [3.53, 4.27] ng/ml
Up to 25th percentile	159 (24.0%)	<2.60 ng/ml
25th-50th percentile	170 (25.8%)	≥2.60 to 3.75 ng/ml
50th-75th percentile	149 (25.2%)	≥3.75 to 5.56 ng/ml
75th-100th percentile	151 (25.0%)	≥5.5 g ng/ml
(ΣPFOA) Branch isomers-perfluorooctanoate and Linear isomer perfluorooctonate		
Geometric mean [95% confidence level]		1.92 [1.74, 2.11] ng/ml
Up to 25th percentile	186 (24.9%)	< 1.39 ng/ml
25th-50th percentile	173 (24.6%)	≥ 1.39 to 1.93 ng/ml

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	N (weighted %)	
50th-75th percentile	136 (21.7%)	≥1.93 to <2.67 ng/ml
75th-100th percentile	135 (28.7%)	≥2.67 ng/ml

[*] The body mass index for children was based upon NHANES determinations.

[†] Values below the lower limit of detection (0.1 ng/ml) were imputed as 0.7 ng/ml ($0.1/\sqrt{2}$) (Hornung, *et al.*, 1990).

[‡] There were too many results below than the lower limit of detection for a valid calculation of the geometric mean.

Σ, sum of.

Table 3

Dental Caries Experience Versus Selected Variables, National Health and Nutrition Examination Survey, 2013–2014

	Dental caries experience whole sample			Dental caries experience for children below limit of detection for perfluorodecanoic acid		
	Yes	**No**	***P*-value**	**Yes**	**No**	***P*-value**
Age in years			**0.0175**			0.3847
≥3 to ≤5	66 (36.0%)	112 (64.0%)		39 (51.1%)	47 (48.9%)	
>5 to ≤11	255 (51.1%)	196 (48.9%)		131 (58.5%)	80 (41.5%)	
Sex			0.2795			0.0664
Female	142 (43.5%)	149 (56.5%)		74 (50.4%)	64 (49.6%)	
Male	179 (48.8%)	159 (51.2%)		96 (62.1%)	63 (37.9%)	
Race/ethnicity			**0.0054**			0.1547
Non-Hispanic white	74 (40.6%)	89 (59.4%)		43 (52.8%)	36 47.2%)	
Non-Hispanic black	75 (45.0%)	84 (55.0%)		37 (46.0%)	40 (54.0%)	
Mexican American	127 (57.5%)	88 (42.5%)		99 (68.9%)	31 (31.1%)	
Other	45 (48.9%)	47 (51.1%)		24 (56.7%)	20 (43.3%)	
Ratio of family income to poverty guidelines			**0.0216**			0.2111
<2.00	224 (52.8%)	167 (47.2%)		112 (60.4%)	71 (40.6%)	
2.00 and above	81 (38.8%)	125 (61.2%)		48(51.9%)	48 (48.1%)	
Missing	16(47.1%)	16(52.9%)				
Body mass index for children *			0.2065			**0.0448**
Underweight/normal weight	198 (43.6%)	206 (56.4%)		110(51.0%)	95 (49.0%)	
Overweight/obese	123 (51.8%)	102 (48.2%)		60 (68.4%)	32 (31.6%)	
Insurance	0.4831	0.6977				
Yes	304 (45.9%)	293 (54.1%)		†	†	
No	17 (52.7%)	15 (47.3%)		†	†	
Tooth brushing frequency			**0.0005**			0.2014
≤1 time per day	117 (52.9%)	92 (47.1%)		63 (61.0%)	38 (39.0%)	
≥2 times per day	204 (42.5%)	215 (57.5%)		107 (52.7%)	89(47.3%)	
Dental visit			**0.0184**			0.0030
Within the previous year	287 48.6	253 51.4		153 (58.7%)	107 (41.4%)	

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	Dental caries experience whole sample					Dental caries experience for children below limit of detection for perfluorodecanoic acid				
	Yes		No		*P*-value	Yes		No		*P*-value
>1 year or no previous care	34	30.2	55	69.8		17 (33.9%)		20 (66.1%)		
Sugar in diet					0.1731					0.4379
<10%	†		†			†		†		
≥10%	†		†			†		†		
Missing	†		†			†		†		
2-N-methyl-perfluorooctane sulfonamide acetic acid					0.8372					
Less than limit of detection	169	47.2	162	52.8						
Detection to 75th percentile	76	43.4	84	56.6						
75th-100th percentile	76	47.3	62	52.7						
Perfluorodecanoic acid					**0.0002**					
Less than limit of detection	151 (37.3%)		181 (62.7%)							
Detection to 75th percentile	69 (56.0%)		49 (44.0%)							
75th-100th percentile	101 (55.9%)		78 (44.1%)							
Perfluornononanoic acid					0.7071					
Up to 25th percentile	80 (44.6%)		80 (55.4%)							
5th-50th percentile	72 (46.7%)		77 (53.3%)							
50th-75th percentile	86 (50.4%)		67 (49.6%)							
75th-100th percentile	83 (43.0%)		84 (57.0%)							
Perfluorohexane sulfonic acid					0.9801					
Up to 25th percentile	92 (45.5%)		75 (54.5%)							
25th-50th percentile	86 (44.5%)		96 (55.5%)							
50th-75th percentile	68 (47.5%)		62 (52.5%)							
75th-100th percentile	75 (47.2%)		75 (52.8%)							
Linear isomer of perfluorooctanoate					0.8181					
Up to 25th percentile	98 (48.9%)		86 (51.1%)							
25th-50th percentile	87 (46.5%)		84 (53.5%)							
50th-75th percentile	70 (42.0%)		80 (58.0%)							
75th-100th percentile	66 (47.5%)		58 (52.5%)							

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	Dental caries experience whole sample			Dental caries experience for children below limit of detection for perfluorodecanoic acid		
	Yes	**No**	***P*-value**	**Yes**	**No**	***P*-value**
Linear isomer of perfluorooctane sulfonate			0.5081			
Up to 25th percentile	74 (42.1%)	83 (57.9%)				
25th-50th percentile	82 (44.9%)	82 (55.1%)				
50th-75th percentile	81 (47.0%)	73 (53.0%)				
75th-100th percentile	84 (50.6%)	70 (49.4%)				
Monomethyl branch isomers			0.8495			
of perfluorooctanesulfonic acid						
Up to 25th percentile	84 (44.9%)	87 (55.1%)				
25th-50th percentile	85 (43.5%)	88 (56.5%)				
50th-75th percentile	73 (48.5%)	65 (51.5%)				
75th-100th percentile	79 (48.0%)	68 (52.0%)				
Monomethyl branch isomers of perfluorooctanesulfonic acid and linear isomer of perfluorooctane sulfonate			0.6812			
Up to 25th percentile	79 (45.7%)	80 (54.3%)				
25th-50th percentile	84 (44.3%)	86 (54.9%)				
50th-75th percentile	72 (45.1%)	77 (55.1%)				
75th-100th percentile	86 (49.8%)	65 (50.2%)				
($^{\Sigma}$PFOA) Branch isomers-perfluorooctanoate and linear isomer perfluorooctonate			0.76136			
Up to 25th percentile	101 (50.5%)	85 (49.5%)				
25th-50th percentile	88 (45.8%)	85 (54.2%)				
50th-75th percentile	61 (40.4%)	75 (59.6%)				
75th-100th percentile	72 (47.4%)	63 (52.6%)				

*The body mass index for children was based upon NHANES determinations.

†Cell size suppression as at least one cell is ≤10.

$^{\Sigma,}$sum of; SE, standard error.

Values below the lower limit of detection (0.1 ng/ml) were imputed as 0.7 ng/ml ($0.1/\sqrt{2}$) (Hornung, et al., 1990).

Results are from Rao-Scott Chi Square analyses utilizing masked pseudo-primary sampling unit, masked variance pseudo-stratum, and survey weights.

Dental caries experience is presented as the outcome variable and the other variables as predictors.

Bold items have P-values <.05.

Table 4

Logistic Regression on Dental Caries Experience With Various Perfluoroalkyls and Other Factors, National Health and Nutrition Examination Survey, 2013–2014

	Unadjusted OR (CI)	*P*-value	Adjusted OR (CI)	*P*-value
2-N-methyl-perfluorooctane sulfonamide acetic acid				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.06 (0.54,2.10)	0.8502	1.60 (0.81, 3.17)	0.1635
Perfluorodecanoic acid				
Less than to 75th percentile	reference		reference	
75th to 100th percentile	**1.71 (1.19, 2.46)**	**0.0069**	1.54 (1.03, 2.30)	0.0385
Perfluornononanoic acid				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.04 (0.71, 1.54)	0.8186	1.09 (0.68, 1.74)	0.6943
Perfluorohexane sulfonic acid				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.05 (0.70, 1.58)	0.8186	0.78 (0.45, 1.34)	0.3429
Linear isomer of perfluorooctanoate				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.07 (0.64, 1.79)	0.7715	1.38 (0.70, 2.70)	0.3248
Linear isomer of perfluorooctane sulfonate				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.27 (0.80, 2.01)	0.2898	1.49 (1.00, 2.24)	0.0535
Monomethyl branch isomers of perfluorooctanesulfonic acid				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.09 (0.65, 1.81)	0.7273	1.30 (0.62, 2.73)	0.4643
(ΣPFOS) Monomethyl branch isomers of perfluorooctanesulfonic acid and linear isomer of perfluorooctane sulfonate				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.21 (0.86, 1.72)	0.2511	1.41 (0.97, 2.05)	0.0694
(ΣPFOA) Branch isomers-perfluorooctanoate and Linear isomer perfluorooctonate				
Less than 75th percentile	reference		reference	
75th to 100th percentile	1.07 (0.57, 2.03)	0.85204	1.33 (0.70, 2.53)	0.3516

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	Unadjusted OR (CI)	*P*-value	Adjusted OR (CI)	*P*-value
Age in years				
≥3 to ≤5	reference		reference	
≥5 to ≤11	**1.85(1.07,3.21)**	**0.0307**	**2.07 (1.17,3.67)**	**0.0163**
Sex				
Female	reference		reference	
Male	1.24 (0.80, 1.92)	0.3069	1.34 (0.84, 2.12)	0.2007
Race/ethnicity				
Non-Hispanic white	reference		reference	
Non-Hispanic black	1.20(0.69,2.11)	0.4986	0.97 (0.56, 1.69)	0.9046
Mexican American	**1.99 (1.26, 3.13)**	**0.0059**	**1.85 (1.13, 3.05)**	**0.0185**
Other	1.40 (0.69, 2.86)	0.3316	1.16 (0.50, 2.68)	0.7116
Ratio of family income to poverty guidelines				
<2.00	**1.76(1.11,2.80)**	**0.0197**	**1.89 (1.27, 2.81)**	**0.0039**
2.00 and above	reference		reference	
Tooth brushing frequency				
≤1 time per day	**1.52(1.14, 2.02)**	**0.0071**	**1.78 (1.23, 2.59)**	**0.0049**
≥2 times per day	reference		reference	
Dental visit				
Within the previous year	**0.46 (0.22, 0.96)**	**0.0409**	**0.43 (0.22, 0.86)**	**0.0195**
>1 year or no previous care	reference		reference	
Fluoride in water (beta)	**0.54 (0.32, 0.92)**	**0.0271**	**0.47 (0.25, 0.87)**	**0.0189**

Σ, sum of; CI, confidence interval; OR, odds ratio.

Dental caries experience is presented as the outcome variable and the other variables as predictors.

Adjusted models are specific for the identified perfluoroalkyl and age, sex, race/ethnicity, ratio of family-income-to-poverty-level guidelines, tooth brushing frequency, dental visit, percentages of sugar in the diet, and fluoride in the water.

The adjusted data concerning the nonperfluoroalkyl factors (age, sex, race/ethnicity, ratio of family-income-to-poverty guidelines, tooth brushing frequency, fluoride, and dental visit) are the relationships from the eligible population associated with perfluorodecanoic acid.

Bold items have P-values <.05.