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# Isomer-Specific Serum Concentrations of Perfluorooctane Sulfonic Acid among U.S. Adults: Results from the National Health and Nutrition Examination Survey (NHANES) and the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS)


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## Abstract

Electrochemical fluorination manufacture of perfluorooctane sulfonic acid (PFOS), one of the most studied per- and polyfluoroalkyl substances, produces mixtures of linear and branched isomers, but little is known about human exposure to linear or branched PFOS isomers. We examined determinants affecting isomer-specific patterns of PFOS in serum in two adult populations in the United States, the National Health and Nutrition Examination Survey



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Supporting Information

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Serum concentrations of *n*- and sm-PFOS in NHANES and SWAN-MPS populations; association of characteristics with % *n*-PFOS in U.S women aged 45–56 years participating in NHANES; selection of the NHANES and SWAN-MPS analytic samples; and adjusted means of *n*-PFOS in U.S. women aged 45–46 years participating in NHANES by site and race/ethnicity (PDF)


Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.2c04501

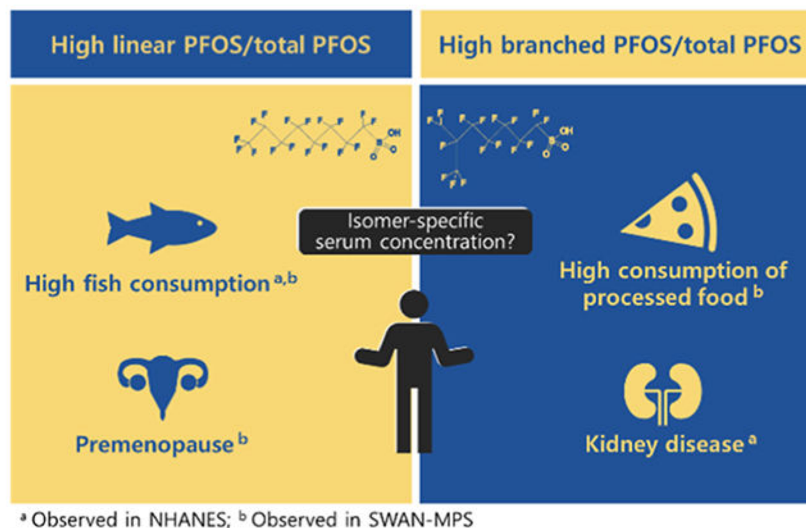


The authors declare no competing financial interest.


The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). The use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.

(NHANES) and the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS). After adjusting for demographic variables, fish consumption (in both populations), a glomerular filtration rate above 90 mL/min/1.73 $m^2$ (observed in NHANES; not tested in SWAN-MPS), premenopausal status (only observed in SWAN-MPS), and less consumption of processed food (observed in SWAN-MPS; not tested in NHANES) were associated with a higher proportion of linear PFOS. Non-Hispanic Black and Asian participants were likely to have a higher proportion of linear PFOS than non-Hispanic White participants in both populations. Our findings suggest that isomer-specific patterns of PFOS serum concentrations in humans vary depending on population characteristics that affect PFOS exposure and excretion. Consideration of specific PFOS isomers in future human biomonitoring and epidemiologic studies can provide useful insight to better understand PFOS exposure.

## Graphical Abstract




### Keywords

PFAS; electrochemical fluorination; branched; seafood; processed food; glomerular filtration; menstruation; menopause

## INTRODUCTION

Since the 1950s, per- and polyfluoroalkyl substances (PFAS) have contaminated the global environment as a result of their manufacturing and application in consumer products and industries.[1] Perfluorooctane sulfonic acid (PFOS), one of the most studied PFAS, has been predominantly detected in environmental samples and human blood. PFOS can cause various adverse health effects in animal models, including endocrine disruption,[2,3] reduced reproduction,[3] and lipid dysregulation.[4] In epidemiologic studies, PFOS exposure has been associated with adverse effects on thyroid function,[5] sex hormone homeostasis,[6] ovarian function,[7] adverse pregnancy and birth outcomes (e.g., preeclampsia, preterm birth),[8] and



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kidney function.[9] PFOS and its salts are classified as persistent organic pollutants, and their production and usage are regulated globally under the Stockholm Convention since 2009.[10]

Electrochemical fluorination (ECF) was a PFAS manufacturing technique until 2002 when 3M company, a major PFAS producer, phased out the production of PFOS and its precursors. ECF yields both linear and branched isomers of PFAS;[11] approximately 30% of PFAS produced by ECF are branched isomers.[12] Consequently, branched isomers of PFOS can account for a considerable portion of the total PFOS in the environment. Nevertheless, the ratio between linear and branched isomers of PFOS can vary depending on geographical factors and types of environmental matrices or biota.[13,14] For example, environmental samples near manufacturing plants had a smaller proportion of linear PFOS (*n*-PFOS) isomers than samples from non-manufacturing areas.[14] The proportion of the linear isomer is higher in soil compared to groundwater, suggesting that isomers may have distinct affinity for soil or water.[15]

Human exposure routes to PFOS include the use of PFOS-containing products,[16,17] consumption of PFOS-contaminated foods[18] and drinking water,[19] and environmental sources of PFOS such as air, soil, and indoor dust.[20–22] Serum elimination half-life of PFOS was estimated to be 3.1 years in women and 4.6 years in men.[23] PFOS is excreted through several pathways, including urine, feces, menstruation, transplacental transfer, and breastfeeding;[24–29] branched PFOS isomers are expected to have higher excretion rates than *n*-PFOS.[27,28]

Recent biomonitoring studies have reported distributions of linear and branched isomers of PFOS.[14,30,31] However, little is known about factors that influence the relative proportion of PFOS isomers. In the present study, we evaluated the associations of isomer-specific PFOS serum concentrations with demographic characteristics, potential exposure sources (e.g., foods, drinking water), and biological factors related to chemical excretion (e.g., glomerular filtration, reproductive factors) using data from the general U.S. population and from a cohort of midlife women.

## MATERIALS AND METHODS

### Study Population 1: The National Health and Nutrition Examination Survey (NHANES).

The National Health and Nutrition Examination Survey (NHANES) is a biannual survey designed to examine the health and nutrition status of the U.S. population.[32] Using complex multistage sampling with oversampling of subgroups, NHANES produces national estimates representative of the total noninstitutionalized civilian U.S. population. NHANES includes a direct home interview with demographic, health, and nutrition-related questions and a standardized physical examination with biospecimen collection in a mobile examination center.[33] As part of NHANES, quantification of serum PFAS, including PFOS, was conducted for a representative 1/3 subset of the samples. For this study, we used data from adults (20–79 years old) who participated in three cycles of NHANES from 2013 to 2018, where PFOS isomers (linear and branched) were determined ($n$ = 15,902); we included only individuals with serum PFOS concentrations ($n$ = 4530). We excluded those having missing

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data on poverty-income ratio, body mass index (BMI), and serum creatinine, yielding a final analytic sample of 3759 individuals (Figure S1a).

### Study Population 2: The Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS).

The Study of Women's Health Across the Nation (SWAN) is a multi-site, multi-ethnic, longitudinal study designed to investigate factors related to the menopausal transition and their links to age-related health outcomes.[34] A total of 3302 women were recruited in the cohort study from 7 study sites in the U.S. between 1996 and 1997. Black women were recruited from Boston, MA; Pittsburgh, PA; Southeast Michigan, MI; and Chicago, IL. Hispanic, Chinese, and Japanese women were recruited from Newark, NJ; Oakland, CA; and Los Angeles, CA, respectively. White women were recruited from all of the seven study sites. Inclusion criteria at baseline included being 42–52 years of age, having an intact uterus and both ovaries, no current use of exogenous hormones affecting the ovarian function, 1 menstrual period in the previous 3 months, and self-identifying with the designated race/ethnic group at a given site. The participants were followed up near-annually through 2016–2017; they answered questionnaire surveys, attended clinic visits, and provided a biological specimen (serum and urine).

SWAN Multi-Pollutant Study (SWAN-MPS), a sub-study of SWAN, was designed to investigate exposure to various environmental pollutants, such as PFAS, persistent organic pollutants, heavy metals, and other endocrine disrupting chemicals, as well as their association with metabolic diseases and reproductive health outcomes in midlife women.[31] SWAN-MPS included four race/ethnic groups (White, Black, Chinese, and Japanese) from five study sites (Boston, Pittsburgh, Southeast Michigan, Oakland, and Los Angeles). PFAS were quantified in serum samples obtained from 1400 participants at SWAN follow-up visit 3 (1999–2000). Those with missing information on education, financial hardship, BMI, parity, and dietary intake ($n = 52$) were excluded from this analytic sample. Participants with postmenopausal status by bilateral salpingo-oophorectomy or hysterectomy ($n = 45$) were also excluded because of the limited sample size, leaving 1303 SWAN-MPS participants in the analytic sample (Figure S1b).

### Quantification of PFOS in Serum.

Quantification of PFOS isomers in the serum of NHANES and SWAN-MPS participants was conducted at the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention (CDC) following analytical approaches previously described.[35,36] Briefly, after diluting the serum with formic acid, PFAS were preconcentrated by online solid-phase extraction. *n*-PFOS and a sum of perfluoromethylheptane sulfonic acid isomers (sm-PFOS) were separated and quantified using high-performance liquid chromatography–isotope dilution tandem mass spectrometry. The isomers known to be included in sm-PFOS are perfluoro-3-methylheptane sulfonate, perfluoro-4-methylheptane sulfonate, perfluoro-5-methylheptane sulfonate (P5MHpS), and perfluoro-6-methylheptane sulfonate. We used P5MHpS and *n*-PFOS as the analytical standards to quantify the concentrations of sm-PFOS and *n*-PFOS, respectively. Total PFOS was calculated as the sum of *n*-PFOS and sm-PFOS. The limit of detection (LOD) for

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both *n*-PFOS and sm-PFOS was 0.1 ng/mL. Non-detectable concentrations were imputed with LOD divided by the square root of 2.[37] The percentage of linear PFOS (% *n*-PFOS) was calculated as the concentration of *n*-PFOS divided by the concentration of total PFOS. The CDC laboratory is certified to comply with the requirements set forth in the Clinical Laboratory Improvement Amendments of 1988 (CLIA′88) and is recertified every 2 years. The analytical measurements of NHANES and SWAN samples were performed following strict quality control/quality assurance CLIA guidelines, including successful participation in external quality assessment schemes [e.g., Arctic Monitoring and Assessment Program (AMAP); https://www.inspq.qc.ca/en/ctq/eqas/amap/description] to demonstrate accuracy and precision.[35] The adequacy of our method for quantifying PFAS (e.g., PFOS) has been confirmed by successful participation in AMAP since 2011, including seven proficiency testing rounds since 2020, when AMAP added sm-PFOS and *n*-PFOS to its list of evaluated PFAS. Furthermore, along with the study samples, each analytical run included high- and low-concentration quality control (QC) materials, analytical standards, and reagent blanks to assure the reliability of the data.[35] The relative standard deviation (RSD) of replicate analyses of QC materials analyzed with the SWAN study samples in a 7 month period were 8.1 and 8.5% (high concentration QC, $N = 67$), and 8.7 and 10.5% (low concentration QC, $N = 67$) for *n*-PFOS and sm-PFOS, respectively. Similar RSDs have been reported for NHANES as described on the NHANES Laboratory Procedure Manuals (e.g., CDC 2020[35]) publicly available on the NHANES website.

Other PFAS, such as perfluorooctanoic acid (PFOA) and perfluorohexane sulfonic acid (PFHxS), were measured in NHANES[35] and SWAN-MPS,[31] and PFOA and PFHxS also have linear and branched isomers.[14] However, we did not include PFOA or PFHxS in this study because the detection frequency of branched PFOA isomers was too low to conduct the statistical analysis, and only the linear isomer of PFHxS was measured.

### Covariates.

NHANES collected data on race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, others), sex, age, female reproductive health (parity, menstrual status), poverty–income ratio, BMI, kidney function, fish and shellfish consumption (during the past 30 days), and source of tap water for drinking (do not drink, community supply, other). We categorized the poverty–income ratio as <1, 1–<1.25, 1.25–<2, 2–<4, and  4, where a higher poverty–income ratio indicates a better financial status. BMI (kg/m$^2$) was calculated as the measured weight (kg) divided by the square of measured height (m). The estimated glomerular filtration rate (eGFR), which indicates kidney function, was calculated using the following CKD-EPI 2021 equation[38]

$$\mathrm{eGFR_{cr}(mL/min/1.73\,m^2)} = 142 \times \min\left(\frac{\mathrm{Scr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\mathrm{Scr}}{\kappa}, 1\right)^{-1.200} \times 0.9938^{\mathrm{Age}} \times 1.012\ [\text{if female}]$$

where Scr is the serum creatinine concentration (mg/dL), $\kappa$ is 0.7 for females and 0.9 for males, and $\alpha$ is −0.241 for females and −0.302 for males. Both continuous and categorized ( 60, >60–90, >90 mL/min/1.73 m$^2$) eGFR were considered. Information on parity (number of deliveries) and menstrual status (having at least one menstrual period in the past 12

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months or not) was self-reported by female participants. To calculate the monthly frequency of fish and shellfish consumption, we summed the self-reported frequencies of each fish and shellfish item consumed in the previous 30 days. We did not consider processed food consumption in the NHANES population which was obtained using 24 h dietary recall interviews.[39]

SWAN-MPS collected data on the study site (Southeast Michigan, Boston, Oakland, Los Angeles, or Pittsburgh), race/ethnicity (White, Black, Chinese, or Japanese), age, parity, menopausal status, education (  high school diploma, some college, college, or postgraduate), financial hardship (hardship to pay for basics; very hard, somewhat hard, or not hard at all), BMI, fish and shellfish consumption, and processed food consumption (pizza, salty snacks, or French fries). Information on financial hardship, dietary consumption, and parity was collected at the baseline of SWAN (visit 0, 1996–1997), while other information was collected at the SWAN-MPS baseline (visit 3, 1999–2000). Education and financial hardship were used as indicators for socioeconomic status because the poverty–income ratio was not available in SWAN-MPS. We calculated parity as the sum of the self-reported number of live births and stillbirths. SWAN classified women into four menopausal stages based on bleeding patterns and surgical history: premenopause if women had experienced at least one menstrual bleed in the last 3 months with no change in bleeding regularity during the last year; early perimenopause if women had experienced at least one menstrual bleeding in the last 3 months with some change in the regularity of bleeding during the last year; late perimenopause if women had experienced no menstrual bleeding in the last 3 months but some menstrual bleeding during the last 11 months; and postmenopause once women had experienced at least 12 consecutive months of amenorrhea. We grouped menopausal status into pre-/early perimenopausal, late peri-/natural postmenopausal, and unknown status due to hormone therapy. Women who were postmenopausal due to surgery were excluded from analyses. The frequency of dietary consumption was obtained using a modified Block food frequency questionnaire.[40–42] Fish and shellfish consumption included fried fish or fish sandwich, tuna, shellfish, and other fish. Japanese participants were additionally asked about the consumption of Japanese-style whole fish or canned fish. To calculate the monthly frequency of fish and shellfish consumption, we summed the monthly frequency of consumption of each item. Monthly frequency of fish and shellfish consumption was considered continuously as well as in weighted tertiles. We categorized frequencies of consumption of pizza, salty snacks (including potato chips, corn chips, popcorn, and crackers), and French fries (including fried potatoes) considering their distributions (never or <1/month, 1/month, or  2/month for pizza and French fries; never or <1/month, 1–2/month, or  1/week for salty snacks). Kidney function and tap water source were not included because there was no information in the SWAN-MPS population.

### Statistical Analysis.

All statistical analyses were conducted using R (version 4.1.1). All analyses of NHANES data accounted for NHANES' complex multistage sampling design with sample weights (subsample weights for PFAS measurement) using the "survey" package (version 4.1). Following NHANES analytical guidelines (https://wwwn.cdc.gov/nchs/data/nhanes/

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analyticguidelines/11-16-analytic-guidelines.pdf), 6 year sample weights were calculated from the 2 year sample weights of each cycle. Because concentrations of *n*-PFOS and sm-PFOS had right-skewed distributions, concentrations were reported as geometric means (GMs); the % *n*-PFOS was reported as the arithmetic mean (AM) based on its normal distribution. Their geometric standard errors (GSEs) or standard errors (SEs) were reported to show the precision of the weighted estimates from the NHANES data because NHANES used sampling weights to represent the U.S. population. On the other hand, SWAN-MPS did not use sampling weights. Therefore, geometric standard deviations (GSDs) or standard deviations (SDs) were reported for the SWAN-MPS data to show variation among the participants. We calculated the GM or AM of *n*-PFOS, sm-PFOS, and % *n*-PFOS by demographic, biological, or dietary factors.

To identify determinants of % *n*-PFOS, we conducted linear regression with each biological or dietary factor as a potential determinant. The first set of models (model 1) was adjusted for demographic factors (survey year, sex, continuous age, and race/ethnicity for NHANES; study site, continuous age, and race/ethnicity for SWAN-MPS). In the second set of models (model 2), socioeconomic status (poverty–income ratio for NHANES and education for SWAN-MPS) and BMI were additionally included. To compare % *n*-PFOS between race/ethnicity or site (only for SWAN-MPS) groups, the least-squared means of each group were calculated based on linear models adjusted for covariates which showed significant associations with % *n*-PFOS in previous linear regression models. Considering the differences in sex composition and age range between the two populations, sex- and age-stratified analyses were conducted with NHANES female participants having the same age range as SWAN-MPS women. Statistical significance was determined at $\alpha = 0.05$.

# RESULTS

## Characteristics of the NHANES Population and Relative Concentrations of PFOS Isomers.

The weighted proportions of each race/ethnic group in the U.S. based on NHANES 2013–2018 (Table 1) were 66% (non-Hispanic White), 15% (Hispanic), 11% (non-Hispanic Black), 5% (non-Hispanic Asian), and 4% (other race). Fifty-one percent of the participants were female, and 63% of the participants had an eGFR greater than 90 mL/min/1.73 $m^2$. Among the female participants, 56% were nulliparous and 49% experienced at least one menstrual period in the past 12 months.

Survey-weighted serum concentrations of *n*- and sm-PFOS and % *n*-PFOS in U.S. adults are shown in Tables 1 and S1. Most (69.0%) of the total PFOS quantified in the serum of NHANES participants was *n*-PFOS. Non-Hispanic Asian persons had the highest % *n*-PFOS (75.1%), closely followed by non-Hispanic Black persons (74.5%). Participants who were female, younger, with a lower poverty–income ratio, who consumed more fish/shellfish, and with a higher eGFR had a higher % *n*-PFOS than other participants.

## Characteristics of the SWAN-MPS Population and Relative Composition of PFOS Isomers.

The proportions of participants in each study site in SWAN-MPS (Table 2) were 27% (Los Angeles), 23% (Oakland), and 17% (Southeast Michigan, Pittsburgh, and Boston). Most

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participants were White (51%), followed by Black (21%), Japanese (15%), and Chinese (13%) persons; 31% of the participants had obesity (BMI  30 kg/m$^2$). Most participants (65%) were in premenopausal or early perimenopausal status.

Serum concentrations of *n*- and sm-PFOS and % *n*-PFOS in SWAN-MPS participants are shown in Tables 2 and S2. Most (70.5%) total PFOS was *n*-PFOS. Participants from Oakland showed the highest % *n*-PFOS (72.6%), followed by Southeast Michigan (72.2%), while those from Los Angeles showed the lowest % *n*-PFOS (68.3%). Participants of non-White race/ethnicity, with lower education, consuming more fish/shellfish, consuming less processed foods (pizza, salty snacks, or French fries), and reporting higher parity were more likely to have higher % *n*-PFOS than other participants. We observed no significant difference in % *n*-PFOS by age group or menopausal status.

### Association of Potential Exposure Sources of PFOS and Biological Characteristics with % *n*-PFOS in NHANES.

Table 3 shows the adjusted difference in % *n*-PFOS by potential exposure sources of PFOS or biological characteristics in NHANES. In general, results were robust regardless of the additional adjustment for the poverty–income ratio and BMI. Fish and shellfish consumption was positively associated with % *n*-PFOS. eGFR >90 mL/min/1.73 m$^2$ was associated with higher % *n*-PFOS. Drinking tap water, parity, and menstruation status did not show any significant associations with % *n*-PFOS.

### Association of Potential Exposure Sources of PFOS and Biological Characteristics with % *n*-PFOS in SWAN-MPS.

Table 4 shows the adjusted difference in % *n*-PFOS by potential dietary exposure sources of PFOS or reproduction-related characteristics in the SWAN-MPS. Regardless of the additional adjustment for education and BMI, results were generally robust. Fish and shellfish consumption, considered both as tertiles and as a continuous measure, were positively associated with % *n*-PFOS. Consumption of pizza, salty snacks, or French fries was inversely associated with % *n*-PFOS. Late perimenopausal/natural postmenopausal women had significantly lower % *n*-PFOS than pre-/early perimenopausal women. We observed no significant association of parity with % *n*-PFOS.

### Difference in % *n*-PFOS by Race/Ethnicity and Site.

In NHANES, non-Hispanic Black participants had the highest adjusted mean of % *n*-PFOS, followed by Asian persons (Figure 1a). Their adjusted means were significantly higher than those of non-Hispanic White participants. A similar trend was observed when the population was restricted to women aged 45–56 years (Figure S2). In the SWAN-MPS, Black, Chinese, or Japanese women had significantly higher adjusted means of % *n*-PFOS than White women in each site (Figure 1b). Among the White participants in different sites, White women in Los Angeles showed the lowest adjusted mean of % *n*-PFOS, which was significantly lower than that observed in Southeast Michigan, Pittsburgh, and Boston women.

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## DISCUSSION

In this study, we investigated determinants of the relative proportion of PFOS isomers (i.e., *n*-PFOS and branched PFOS) in human serum in two U.S. populations: NHANES and SWAN-MPS. Our findings show that frequent consumption of fish/shellfish was a significant determinant of a higher proportion of *n*-PFOS in both NHANES and SWAN-MPS. eGFR  60 mL/min/1.73 $m^2$ in NHANES as well as frequent consumption of processed foods and late peri-/postmenopausal status in SWAN-MPS were significant determinants of lower proportion of *n*-PFOS. We also found a significant difference in the relative ratio of PFOS isomers among race/ethnicity and study site groups even after adjusting for other significant determinants, suggesting that additional factors may influence isomer-specific serum concentrations of PFOS in humans.

The differences we observed in the relative ratios of PFOS isomers by biological factors (i.e., eGFR, menopausal status, and so forth) may relate to the isomer-specific binding of PFOS to serum proteins. Beesoon and Martin[43] estimated a stronger binding affinity of the linear PFOS isomer to human serum albumin compared to branched PFOS isomers based on a biochemical experiment with an ultrafiltration method. Therefore, a substantial fraction of *n*-PFOS bound to serum albumin might not be filtered through the glomerulus in the kidney, resulting in relatively higher fractions of branched PFOS isomers excreted in urine compared to *n*-PFOS.[43] This is further supported by observations that several major branched PFOS isomers displayed higher renal clearance in humans than *n*-PFOS (0.045–0.072 mL/day/kg for branched PFOS vs 0.031–0.045 mL/day/kg for *n*-PFOS),[27] in concordance with the explanation by isomer-specific binding to albumin. Our finding in NHANES that people with a higher rate of glomerular filtration had a higher proportion of linear PFOS in their serum agrees with the previous understanding of isomer-specific renal excretion of PFOS.

Similar to glomerular filtration, menstruation and transplacental transfer are elimination routes of PFOS. We hypothesize that menstruation or transplacental transfer in women contributes to the excretion of PFOS in a branched isomer-selective manner.[28,43] In SWAN-MPS, we observed that women who were late peri-/natural postmenopausal had a statistically significant lower proportion of linear PFOS than women who were pre-/early perimenopausal. However, we did not find any statistically significant associations for parity in either study or for menstrual status in NHANES. Participants in NHANES spanned ages 20–79 years, and so the measure of menstrual status may not have been sensitive enough to correctly reflect menstrual patterns, which vary dramatically by age. Indeed, when the analysis in NHANES was restricted to female participants aged 45–56 years, the age range of SWAN-MPS participants, we found a statistically significant association between menstruation status and % *n*-PFOS (Table S3).Also, the classification of menstrual status in NHANES participants was based on one question related to having at least one menstrual period in the past 12 months, which might have been a source of misclassification, compared to the prospective classification of menopausal status in SWAN, based on multiple detailed bleeding questions. Regarding parity, in a population of Norwegian pregnant women and their infants, the women had a lower ratio of branched PFOS versus *n*-PFOS isomers in their serum as compared to the infants at 6 months after the birth, thereby suggesting

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higher transfer of branched PFOS isomers during pregnancy and the postpartum period compared to the linear isomer.[44] Considering the scientific evidence supporting the selective transfer of branched PFOS isomers and the significant association of menopausal status on % *n*-PFOS observed in SWAN-MPS, further research can help increase the understanding on the potential association between reproduction-related factors and isomer-specific excretion of PFOS.

It is noteworthy that both the NHANES and SWAN-MPS populations consistently showed a positive association of fish consumption with the relative proportion of *n*-PFOS. It has been reported that *n*-PFOS preferentially accumulates over branched isomers in animals such as cattle,[45] the chicken embryo,[46] and white-tailed eagle nestlings.[47] Similarly, higher bioaccumulation capacity was observed for *n*-PFOS than branched PFOS isomers in a fish experiment.[48] The relatively high accumulation of *n*-PFOS in fish and the importance of fish consumption as a source of PFOS exposure[16,18,31] support our observation of the relationship between fish consumption and an increased proportion of *n*-PFOS in serum in NHANES and SWAN-MPS.

Given that PFAS have been used in food packaging,[49,50] and intake of processed foods is one of the important sources of PFOS exposure,[18,31] the isomeric distribution of PFOS in serum can be affected by the amount of processed foods consumed. In SWAN-MPS, we found that women consuming processed foods frequently had a higher proportion of branched PFOS isomers than other women. Additional research can provide useful data to increase our understanding of the existing limited information on PFOS isomer profiles in these foods or packaging.

Interestingly, we found racial/ethnic differences in the isomer composition even after adjusting for the important variables identified in this study. In SWAN-MPS, Black women had a significantly higher proportion of the linear PFOS isomer than White women within the study sites. These findings agree with a significantly higher proportion of the *n*-PFOS isomer in non-Hispanic Black persons than in non-Hispanic White persons in NHANES. In addition, in SWAN-MPS, Japanese and Chinese women had a significantly higher proportion of the *n*-PFOS isomer than White women in Los Angeles and Oakland, respectively, in concordance with a similar finding observed between non-Hispanic Asian and non-Hispanic White persons in NHANES. These significant associations of race/ethnicity suggest that there might be additional determinants of isomer composition related to race/ethnicity. We did not have any information on the use of PFAS-containing consumer products in both populations, and this type of consumer product use can be a possible determinant of a higher proportion of branched PFOS.

We also found geographical differences in the SWAN-MPS population, which may relate to isomer-specific local exposure sources which could not be accounted for in this study. Contamination of drinking water by PFAS use in industries or military training camps can be such a local source of PFOS exposure,[22,31] contributing, at least in part, to the geographical differences in the isomer composition in the serum. Several states in the USA have their own regulations on PFAS contamination in drinking water and use in firefighting foams,

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food packaging, or consumer products,[22,51] which may also contribute to geographical differences in PFOS exposure.

Temporal changes in the dominant PFAS manufacturing process may be reflected in % *n*-PFOS. ECF, which was the dominant process before 2000, produces a mixture of linear and branched isomers (approximately 7:3 ratio), whereas telomerization, the dominant process after 2000, yields primarily linear PFOS.[52] However, we found little differences in % *n*-PFOS within the NHANES cycles as well as between the NHANES and the SWAN-MPS participants, whose blood samples were collected a decade apart. It is unclear why the average percentage of liner isomers in blood in these two populations remained similar even after the telomerization process became dominant, but other studies have reported a wide range of % *n*-PFOS from approximately 50 to 75%.[14] Well-developed biomonitoring programs (e.g., continuous monitoring of PFOS isomers in the future NHANES cycles) are warranted to understand a temporal trend in the isomer composition of PFOS in serum.

This study has several strengths. First, the findings on fish and shellfish consumption and race/ethnicity were replicated in the two U.S. adult study populations (one that is nationally representative) with different sampling periods, where the findings in SWAN-MPS reflect exposures before the changes in manufacturing practices, while the findings in NHANES may reflect exposures even a decade after the changes. This highlights the robustness and reliability of our findings. Second, quantification of PFOS isomers in serum from the two populations was performed with the same method and by the same laboratory, which minimizes bias when comparing the measurements between the study populations. Lastly, menopausal status in SWAN-MPS participants was prospectively assessed using bleeding questions. This accurate measurement potentially prevented misclassification bias.

However, there are limitations. First, because of lack of available analytical standards for individual branched PFOS, we relied on the sm-PFOS. Because the toxicokinetics of the different isomers can vary,[27] caution should be taken in the interpretation of the study results. Second, two study populations used different tools to assess fish/shellfish consumption and menopausal or menstrual status, which makes the results of these factors less comparable. Third, the SWAN-MPS participants did not have information on eGFR, which is one of the critical factors for PFOS elimination. However, the impact of kidney dysfunction may be small given the age of SWAN-MPS participants (45–56 years). The prevalence of kidney dysfunction (eGFR <60 mL/min/1.73 $m^2$) in NHANES 2013–2018 participants with the same age range was <2%. Lastly, we relied on serum concentrations of PFOS as an exposure biomarker, which does not provide information on the time elapsed between exposure and serum collection. Therefore, even two participants currently having the same % *n*-PFOS can have experienced different exposure trajectories, which makes it complicated to interpret the results.

In conclusion, the findings of this study suggest that isomer-specific patterns of PFOS serum concentrations in humans can vary depending on population characteristics, such as consumption of dietary sources of PFOS and endogenous physiological factors that affect PFOS excretion (kidney function and menopause). Isomer separation of PFOS and other isomeric PFAS in human biomonitoring and epidemiologic studies can help

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identify additional determinants of isomer-specific exposure and excretion and evaluate isomer-specific adverse health effects.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS

| | |
|---|---|
| **AM** | arithmetic mean |
| **BMI** | body mass index |
| **ECF** | electrochemical fluorination |
| **eGFR** | estimated glomerular filtration rate |
| **GM** | geometric mean |
| **LOD** | limit of detection |
| **NHANES** | National Health and Nutrition Examination Survey |
| ***n*-PFOS** | linear PFOS |

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| | |
|---|---|
| **PFAS** | per- and polyfluoroalkyl substances |
| **PFOS** | perfluorooctane sulfonic acid |
| **sm-PFOS** | sum of perfluoromethylheptane sulfonic acid isomers |
| **SWAN** | Study of Women's Health Across the Nation |
| **SWAN-MPS** | SWAN Multi-Pollutant Study |
| **% *n*-PFOS** | percentage of linear PFOS |

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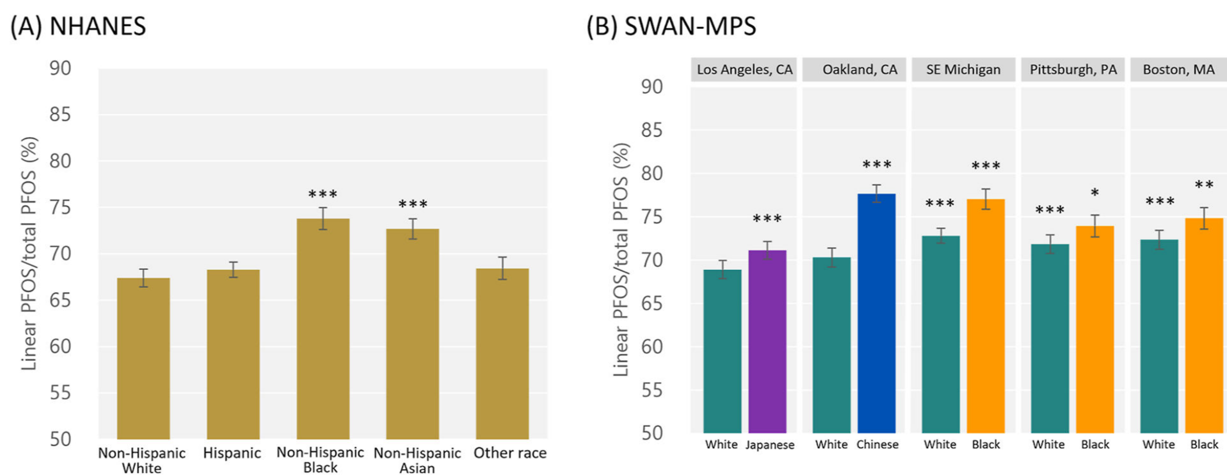


**Figure 1.**

Least-squared means and standard errors of % *n*-PFOS (A) in U.S. adults (NHANES) by race/ethnicity and (B) in the SWAN-MPS population by site and race/ethnicity. The least-squared means were adjusted for covariates with statistical significance in Tables 1 and 2 (NHANES: sex, age, poverty–income ratio, BMI, fish and shellfish consumption, tap water source, and eGFR; SWAN-MPS: education, financial hardship, BMI, fish and shellfish consumption, pizza, salty snacks, and French fries consumption, and parity). In the NHANES population, symbols above the bars indicate a statistical difference compared with non-Hispanic White. Symbols for non-White in the SWAN-MPS population indicate a statistical difference compared with White within each site. Symbols for White in the SWAN-MPS population indicate a statistical difference compared with White in Los Angeles, CA. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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**Table 1.**

Survey-Weighted Relative Percentage of *n*-PFOS (% *n*-PFOS) in U.S. Adults: NHANES 2013–2018

| | | | % *n*-PFOS | |
|---|---|---|---|---|
| | ***n*** | **weighted %** | **mean (SE[a])** | ***p*-value** |
| Total | 3759 | 100 | 69.0 (0.4) | |
| Survey Year | | | | |
| 2013–2014 | 1261 | 33 | 69.5 (0.7) | (ref.) |
| 2015–2016 | 1292 | 34 | 67.9 (0.8) | 0.15 |
| 2017–2018 | 1206 | 33 | 69.6 (0.6) | 0.92 |
| Race/Ethnicity | | | | |
| non-Hispanic White | 1396 | 66 | 67.5 (0.4) | (ref.) |
| Hispanic | 958 | 15 | 69.6 (0.5) | 0.001 |
| non-Hispanic Black | 831 | 11 | 74.5 (0.8) | <0.0001 |
| non-Hispanic Asian | 421 | 5 | 75.1 (0.8) | <0.0001 |
| other race | 153 | 4 | 69.0 (0.9) | 0.12 |
| Sex | | | | |
| male | 1786 | 49 | 67.1 (0.5) | (ref.) |
| female | 1973 | 51 | 70.8 (0.4) | <0.0001 |
| Age (Years) | | | | |
| 20–29 | 645 | 19 | 72.0 (0.4) | (ref.) |
| 30–39 | 684 | 19 | 70.2 (0.6) | 0.002 |
| 40–49 | 665 | 18 | 68.9 (0.6) | <0.0001 |
| 50–59 | 655 | 20 | 68.1 (0.7) | <0.0001 |
| 60–69 | 714 | 16 | 66.7 (0.7) | <0.0001 |
| 70–79 | 396 | 8 | 66.3 (0.7) | <0.0001 |
| Poverty–Income Ratio | | | | |
| <1 | 781 | 14 | 71.2 (0.9) | (ref.) |
| 1–<1.25 | 322 | 6 | 70.4 (0.7) | 0.38 |
| 1.25–<2 | 680 | 15 | 70.1 (0.6) | 0.22 |
| 2–<4 | 986 | 27 | 68.6 (0.5) | 0.002 |
| 4 | 990 | 39 | 68.0 (0.5) | 0.0001 |
| BMI[b] ($kg/m^2$) | | | | |
| <25 | 1017 | 28 | 70.2 (0.6) | (ref.) |
| 25–<30 | 1183 | 32 | 69.2 (0.4) | 0.02 |
| 30 | 1559 | 41 | 68.1 (0.5) | <0.0001 |
| Fish and Shellfish Consumption | | | | |
| tertile 1( 2/month) | 1676 | 45 | 67.7 (0.5) | (ref.) |
| tertile 2(3–5/month) | 907 | 24 | 68.8 (0.6) | 0.06 |
| tertile 3( 6/month) | 1155 | 30 | 71.1 (0.5) | <0.0001 |
| missing | 21 | 0 | | |
| Tap Water Source | | | | |
| do not drink | 833 | 16 | 70.8 (0.6) | (ref.) |

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| | | | % *n*-PFOS | |
|---|---|---|---|---|
| | ***n*** | **weighted %** | **mean (SE[a])** | ***p*-value** |
| community supply | 2480 | 70 | 68.6 (0.5) | 0.001 |
| others | 322 | 12 | 69.1 (0.9) | 0.90 |
| missing | 124 | 2 | | |
| eGFR[c] | | | | |
| 60 mL/min/1.73 $m^2$ | 201 | 6 | 65.8 (1.0) | (ref.) |
| >60–90 mL/min/1.73 $m^2$ | 1079 | 28 | 67.3 (0.5) | 0.11 |
| >90 mL/min/1.73 $m^2$ | 2479 | 68 | 70.0 (0.5) | 0.0003 |
| Parity (Women Only) | | | | |
| 0 | 1004 | 56 | 70.9 (0.5) | (ref.) |
| 1 | 835 | 44 | 70.4 (0.5) | 0.41 |
| Last Menstruation (Women Only) | | | | |
| 12 month | 872 | 49 | 73.3 (0.5) | (ref.) |
| >12 month | 967 | 51 | 68.2 (0.6) | <0.0001 |

[a]Standard error (SE) was reported to show precision of the weighted estimates.

[b]Body mass index.

[c]Estimated glomerular filtration rate.

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**Table 2.**

Serum Concentrations of *n*- and sm-PFOS and Relative Percentage of *n*-PFOS (% *n*-PFOS) in the SWAN-MPS Population

| | | % *n*-PFOS | |
|---|---|---|---|
| | ***n*** **(%)** | **mean (SD[a])** | ***p*****-value** |
| Total | 1303 (100) | 70.5 (6.8) | |
| Site | | | |
| Los Angeles, CA | 346 (27) | 68.3 (6.1) | (ref.) |
| Oakland, CA | 295 (23) | 72.6 (8.1) | <0.0001 |
| Southeast Michigan | 228 (17) | 72.2 (6.5) | <0.0001 |
| Pittsburgh, PA | 219 (17) | 69.6 (6.3) | 0.03 |
| Boston, MA | 215 (17) | 70.4 (5.4) | 0.0004 |
| Race/Ethnicity | | | |
| White | 659 (51) | 68.3 (6.0) | (ref.) |
| Black | 276 (21) | 72.7 (6.2) | <0.0001 |
| Chinese | 169 (13) | 76.6 (7.3) | <0.0001 |
| Japanese | 199 (15) | 69.8 (5.7) | 0.002 |
| Age (Years) | | | |
| >44–48 | 443 (34) | 70.2 (7.3) | (ref.) |
| >48–52 | 603 (46) | 70.8 (6.3) | 0.14 |
| >52–56 | 257 (20) | 70.5 (7.3) | 0.51 |
| Education | | | |
| high school diploma | 236 (18) | 72.0 (8.0) | (ref.) |
| some college | 415 (32) | 70.6 (6.8) | 0.01 |
| college | 318 (24) | 70.4 (6.8) | 0.007 |
| postgraduate | 334 (26) | 69.5 (5.8) | <0.0001 |
| Financial Hardship | | | |
| very hard | 83 (6) | 72.1 (6.8) | (ref.) |
| somewhat hard | 318 (24) | 70.8 (7.4) | 0.13 |
| not hard at all | 902 (69) | 70.3 (6.6) | 0.02 |
| BMI ($kg/m^2$)[b] | | | |
| <25 | 555 (43) | 71.4 (7.0) | (ref.) |
| 25–<30 | 350 (27) | 70.5 (6.6) | 0.04 |
| 30 | 398 (31) | 69.3 (6.7) | <0.0001 |
| Fish and Shellfish Consumption | | | |
| tertile 1( 4.5/month) | 466 (36) | 69.3 (6.2) | (ref.) |
| tertile 2(>4.5–8.5/month) | 417 (32) | 70.4 (6.9) | 0.02 |
| tertile 3(>8.5/month) | 420 (32) | 71.9 (7.1) | <0.0001 |
| Pizza Consumption | | | |
| never or <1/month | 286 (22) | 72.3 (8.1) | (ref.) |
| 1/month | 399 (31) | 70.6 (6.5) | 0.001 |
| 2/month | 618 (47) | 69.6 (6.2) | <0.0001 |

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| | | **% *n*-PFOS** | |
|---|---|---|---|
| | ***n* (%)** | **mean (SD[a])** | ***p*-value** |
| Salty Snack Consumption | | | |
| never or <1/month | 228 (17) | 73.3 (7.6) | (ref.) |
| 1–2/month | 187 (14) | 72.2 (6.5) | 0.1 |
| 1/week | 888 (68) | 69.5 (6.4) | <0.0001 |
| French Fries Consumption | | | |
| never or <1/month | 368 (28) | 71.5 (7.2) | (ref.) |
| 1/month | 283 (22) | 71.0 (6.8) | 0.36 |
| 2/month | 652 (50) | 69.8 (6.5) | 0.0001 |
| Parity | | | |
| 0 | 253 (19) | 69.1 (6.1) | (ref.) |
| 1–2 | 684 (52) | 70.7 (7.2) | 0.002 |
| 3 | 366 (28) | 71.1 (6.5) | 0.0005 |
| Menopausal Status | | | |
| pre-/early perimenopausal | 844 (65) | 70.8 (6.7) | (ref.) |
| late peri-/natural postmenopausal | 260 (20) | 69.9 (6.5) | 0.05 |
| unknown (hormone therapy) | 199 (15) | 70.1 (7.7) | 0.21 |

[a]Standard deviation.

[b]Body mass index.

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**Table 3.**

Association of Characteristics with % *n*-PFOS in U.S. Adults: NHANES 2013–2018

| | | model 1[a] | | model 2[b] | |
|---|---|---|---|---|---|
| | *N* | $\beta$ (95% CI) | *p*-value | $\beta$ (95% CI) | *p*-value |
| Fish and Shellfish Consumption | | | | | |
| continuous (80th vs 20th) | 3738 | 1.9 (1.3, 2.5) | <0.0001 | 2.0 (1.4, 2.6) | <0.0001 |
| tertile 1( 2/month) | 1676 | (ref.) | | (ref.) | |
| tertile 2(3–5/month) | 907 | 1.5 (0.5, 2.6) | 0.004 | 1.7 (0.7, 2.8) | 0.002 |
| tertile 3( 6/month) | 1155 | 3.5 (2.5, 4.6) | <0.0001 | 3.6 (2.8, 4.8) | <0.0001 |
| Tap Water Source | | | | | |
| do not drink | 833 | (ref.) | | (ref.) | |
| community supply | 2480 | −1.0 (−2.2, 0.1) | 0.08 | −0.9 (−2.1, 0.3) | 0.14 |
| others | 322 | 0.9 (−1.1, 2.9) | 0.36 | 1.0 (−1.0, 3.1) | 0.30 |
| eGFR[c] | | | | | |
| continuous (80th vs 20th) | 3759 | 1.9 (0.9, 2.8) | 0.0003 | 1.9 (0.9, 2.8) | 0.0005 |
| 60 mL/min/1.73 $m^2$ | 201 | (ref.) | | (ref.) | |
| >60–90 mL/min/1.73 $m^2$ | 1079 | 1.4 (−0.4, 3.2) | 0.13 | 1.4 (−0.4, 3.3) | 0.13 |
| >90 mL/min/1.73 $m^2$ | 2479 | 2.6 (0.5, 4.7) | 0.02 | 2.7 (0.5, 4.8) | 0.02 |
| Parity (Women Only) | | | | | |
| 0 | 1004 | (ref.) | | (ref.) | |
| 1 | 835 | 0.0 (−1.4, 1.3) | 0.98 | 0.0 (−1.3, 1.4) | 0.96 |
| Last Menstruation (Women Only) | | | | | |
| 12 month | 872 | (ref.) | | (ref.) | |
| >12 month | 967 | −1.7 (−3.6, 0.2) | 0.08 | −1.7 (−3.5, 0.1) | 0.07 |

[a]Adjusted for sex, age, and race/ethnicity.

[b]Additionally adjusted for poverty–income ratio and BMI.

[c]Estimated glomerular filtration rate.

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**Table 4.**

Association of Characteristics with % *n*-PFOS in the SWAN-MPS Population

| | | model 1[a] | | model 2[b] | |
|---|---|---|---|---|---|
| | ***n*** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** |
| Fish and Shellfish Consumption | | | | | |
| continuous (80th vs 20th) | 1303 | 1.1 (0.6, 1.5) | <0.0001 | 1.1 (0.7, 1.6) | <0.0001 |
| tertile 1( 4.5/month) | 466 | (ref.) | | (ref.) | |
| tertile 2(<4.5–8.5/month) | 417 | 0.7 (−0.1, 1.5) | 0.09 | 0.8 (0.0, 1.6) | 0.05 |
| tertile 3( 8.5/month) | 420 | 1.8 (1.0, 2.6) | <0.0001 | 2.0 (1.2, 2.8) | <0.0001 |
| Pizza Consumption | | | | | |
| never or <1/month | 286 | (ref.) | | (ref.) | |
| 1/month | 399 | −1.1 (−2.0, −0.1) | 0.03 | −0.9 (−1.8, 0.0) | 0.06 |
| 2/month | 618 | −1.3 (−2.2, −0.4) | 0.005 | −1.1 (−2.0, −0.2) | 0.02 |
| Salty Snacks Consumption | | | | | |
| never or <1/month | 228 | (ref.) | | (ref.) | |
| 1–2/month | 187 | −0.5 (−1.6, 0.7) | 0.44 | −0.2 (−1.4, 0.9) | 0.71 |
| 1/week | 888 | −2.6 (−3.5, −1.7) | <0.0001 | −2.3 (−3.2, −1.4) | <0.0001 |
| French Fries Consumption | | | | | |
| never or <1/month | 368 | (ref.) | | (ref.) | |
| 1/month | 283 | −0.2 (−1.2, 0.7) | 0.65 | −0.1 (−1.0, 0.9) | 0.88 |
| 2/month | 652 | −1.4 (−2.2, −0.6) | 0.0009 | −1.1 (−1.9, −0.3) | 0.01 |
| Parity | | | | | |
| 0 | 253 | (ref.) | | (ref.) | |
| 1–2 | 684 | 0.7 (−0.2, 1.6) | 0.13 | 0.5 (−0.4, 1.4) | 0.27 |
| 3 | 366 | 0.7 (−0.3, 1.7) | 0.17 | 0.5 (−0.5, 1.6) | 0.29 |
| Menopausal Status | | | | | |
| pre-/early perimenopausal | 844 | (ref.) | | (ref.) | |
| late peri-/natural postmenopausal | 260 | −1.2 (−2.1, −0.3) | 0.01 | −1.3 (−2.2, −0.3) | 0.007 |
| unknown (hormone therapy) | 199 | −0.2 (−1.2, 0.8) | 0.72 | −0.3 (−1.3, 0.7) | 0.53 |

[a]Adjusted for site, age, and race/ethnicity.

[b]Additionally adjusted for education and BMI.