



# Per- and polyfluoroalkyl substances and incident diabetes in midlife women: the Study of Women's Health Across the Nation (SWAN)

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## Abstract

**Aims/hypothesis** Diabetogenic effects of per- and polyfluoroalkyl substances (PFAS) have been suggested. However, evidence based on prospective cohort studies is limited. We examined the association between serum PFAS concentrations and incident diabetes in the Study of Women's Health Across the Nation Multi-Pollutant Study (SWAN-MPS).

**Methods** We included 1237 diabetes-free women aged 45–56 years at baseline (1999–2000) who were followed up to 2017. At each follow-up visit, women with incident diabetes were identified by the presence of one or more of the following conditions: (1) use of a glucose-lowering medication at any visit; (2) fasting glucose  $\geq 7$  mmol/l on two consecutive visits while not on steroids; and (3) any two visits with self-reported diabetes and at least one visit with fasting blood glucose  $\geq 7$  mmol/l. Serum concentrations of 11 PFAS were quantified by online solid-phase extraction–HPLC–isotope dilution–tandem MS. Seven PFAS with high detection rates ( $>96\%$ ) (n-perfluorooctanoic acid [n-PFOA], perfluorononanoic acid [PFNA], perfluorohexane sulfonic acid [PFHxS], n-perfluorooctane sulfonic acid [n-PFOS], sum of perfluoromethylheptane sulfonic acid isomers [Sm-PFOS], 2-[N-methyl-perfluorooctane sulfonamido] acetic acid [MeFOSAA] and 2-[N-ethyl-perfluorooctane sulfonamido] acetic acid) were included in data analysis. Cox proportional hazards models were used to compute HRs and 95% CIs. Quantile-based g-computation was used to evaluate the joint effects of PFAS mixtures.

**Results** After adjustment for race/ethnicity, site, education, smoking status, alcohol consumption, total energy intake, physical activity, menopausal status and BMI, the HR (95% CI) comparing the lowest with the highest tertile was 1.67 (1.21, 2.31) for n-PFOA ( $p_{\text{trend}} = 0.001$ ), 1.58 (1.13, 2.21) for PFHxS ( $p_{\text{trend}} = 0.003$ ), 1.36 (0.97, 1.90) for Sm-PFOS ( $p_{\text{trend}} = 0.05$ ), 1.85 (1.28, 2.67) for MeFOSAA ( $p_{\text{trend}} = 0.0004$ ) and 1.64 (1.17, 2.31) for the sum of four common PFAS (n-PFOA, PFNA, PFHxS and total PFOS) ( $p_{\text{trend}} = 0.002$ ). Exposure to seven PFAS as mixtures was associated with an HR of 2.62 (95% CI 1.12, 6.20), comparing the top with the bottom tertiles for all seven PFAS.

**Conclusions/interpretation** This study suggests that PFAS may increase diabetes risk in midlife women. Reduced exposure to these 'forever and everywhere chemicals' may be an important preventative approach to lowering population-wide diabetes risk.

**Keywords** Diabetes · Midlife women · Per- and polyfluoroalkyl substances · PFAS · Prospective cohort

## Abbreviations

CDC	Centers for Disease Control and Prevention	IPW	Inverse probability weighting
EtFOSAA	2-(N-ethyl-perfluorooctane sulfonamido) acetic acid	LOD	Limit of detection
		MeFOSAA	2-(N-methyl-perfluorooctane sulfonamido) acetic acid

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## Research in context

### What is already known about this subject?

- Per- and polyfluoroalkyl substances (PFAS) are ubiquitous, synthetic compounds widely used in industrial and consumer applications
- PFAS are of public health concern because they are very persistent in the environment and in the human body
- PFAS have been suggested as potential diabetogens owing to their structural similarity to fatty acids

### What is the key question?

- Does exposure to PFAS increase the risk of incident diabetes?

### What are the new findings?

- Higher serum concentrations of certain PFAS were associated with higher risk of incident diabetes in midlife women
- The joint effects of PFAS mixtures were greater than those for individual PFAS, suggesting a potential additive or synergistic effect of multiple PFAS on diabetes risk

### How might this impact on clinical practice in the foreseeable future?

- It is important for clinicians to be aware of PFAS as unrecognised risk factors for diabetes and to be prepared to counsel patients in terms of sources of exposure and potential health effects

MPS	Multi-Pollutant Study
NHS-II	Nurses' Health Study-II
n-PFOA	Linear PFOA
n-PFOS	Linear PFOS
PFAS	Per- and polyfluoroalkyl substances
PFDA	Perfluorodecanoic acid
PFDoDA	Perfluorododecanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFUnDA	Perfluoroundecanoic acid
PPAR	Peroxisome proliferator-activated receptor
Sb-PFOA	Sum of branched PFOA isomers
Sm-PFOS	Sum of perfluoromethylheptane sulfonic acid isomers
SWAN	Study of Women's Health Across the Nation

## Introduction

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous, synthetic compounds used in industrial and consumer applications, such as non-stick cookware, food packaging and food contact materials, carpeting, apparels and firefighting foams [1, 2]. These chemicals, especially long-chain PFAS such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), are of public health concern because they are very persistent in the environment and in the human body [1, 2].

Recently, these chemicals received attention because they were detected in drinking water, affecting more than 200 million residents in the USA [3]. PFAS have, therefore, been detected in the blood of almost all people tested in the USA [4, 5]. The text box summarises potential sources of human exposure to PFAS. A recent review suggests that PFOA, PFOS and other PFAS may be associated with pre-eclampsia, altered hepatic enzyme levels, increased serum lipids, decreased antibody response to vaccines and low birthweight, although their causal relationships need to be assessed [1].

## Sources of human exposure to PFAS

- Drinking contaminated water (from wastewater, firefighting foams, etc.)
- Eating contaminated food (e.g. fish)
- Using consumer products containing PFAS:
  - Non-stick cookware
  - Food packaging and food contact materials (grease-resistant paper, fast food wrappers, microwave popcorn bags)
  - Stain-resistant carpeting and upholstery
  - Waterproof clothing
  - Personal care products and cosmetics

PFAS have also been suggested as potential diabetogens [6]. The structure of PFAS ( $C_nF_{2n+1}-R$ ) consists of perfluoroalkyl chain ( $C_nF_{2n+1}$ ) with an attached functional group (R), either carboxylic ( $-COOH$ ) or sulfonic acids ( $-SO_3H$ ) [7]. Figure 1 illustrates the structures of PFOA and PFOS. Their structures are similar to that of fatty acids, which contain a hydrocarbon chain and carboxylic acid group. PFAS, therefore, have chemical properties similar to those of fatty acids, well-known endogenous ligands of peroxisome proliferator-activated receptors (PPARs) [8]. Known as lipid and insulin sensors, PPARs are main regulators of adipocyte differentiation and lipid and glucose homeostasis [8]. A major physiological pathway through which PFAS may affect diabetes risk is interference with PPARs, resulting in activation or inhibition of PPARs [9]. Experimental studies suggest that PFAS at human-relevant exposure levels may promote adipocyte proliferation and differentiation through PPAR $\alpha$  and/or PPAR $\gamma$  and play a role in inflammation, and lipid and glucose metabolism [10, 11]. Epidemiological evidence of the association between PFAS and type 2 diabetes is limited. Cross-sectional [12–16] and case–control studies with prevalent cases [17, 18] are subject to reverse causality given that reduced kidney function, a well-known complication of diabetes, may lead to accumulation of circulating PFAS due to decreased PFAS excretion [19, 20]. There are mixed findings in prospective studies, with two studies reporting positive associations of PFOS and/or PFOA with incident type 2 diabetes [21, 22], and others reporting no associations [23, 24]. More evidence from population-based prospective cohort

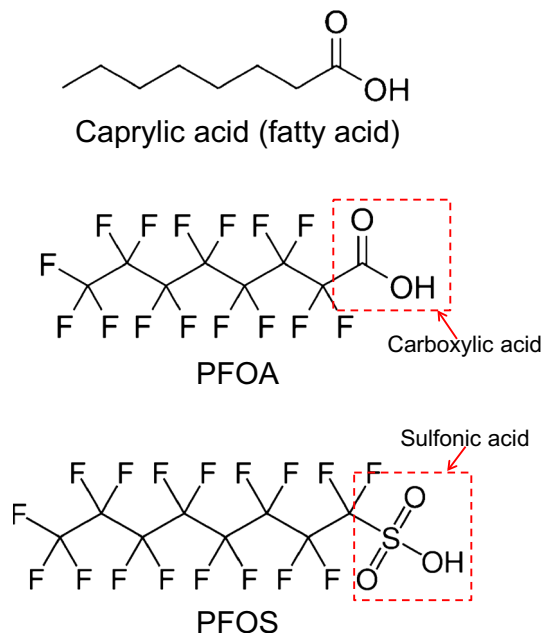
studies is needed to determine causal links between PFAS exposures and diabetes.

The aim of the present study was to examine the association between serum PFAS concentrations and incident diabetes in the Study of Women's Health Across the Nation (SWAN). We also evaluated the overall joint effect of PFAS mixtures to determine whether the overall joint effect is greater than the associations for individual PFAS [25, 26].

## Methods

**Study population** SWAN is an ongoing, multi-site, multi-ethnic, community-based prospective cohort study of midlife women to characterise the menopausal transition and its association with subsequent health endpoints (<http://www.swanstudy.org>) [27]. In 1996–1997, 3302 premenopausal women were recruited at seven study sites in the USA. White women were recruited at each site and women of other races/ethnicities were recruited as follows: Black women from Boston, MA, Pittsburgh, PA, southeast Michigan and Chicago, IL; Hispanic women from Newark, NJ; Chinese women from Oakland, CA; and Japanese women from Los Angeles, CA. Eligibility criteria for the SWAN included age 42–52 years, having an intact uterus, having at least one ovary, having at least one menstrual period, no use of hormone therapy in the past 3 months, and self-identifying with the designated racial/ethnic groups. Participants returned for regular clinical examinations approximately annually. The institutional review board at each participating site approved the study protocol, and all participants provided written informed consent at each study visit.

The SWAN-Multi-Pollutant Study (MPS) was initiated to evaluate the roles of multiple environmental pollutants in chronic diseases during and after the menopausal transition. Environmental chemical exposure assessment, including PFAS, was conducted using repository serum and urine samples from the third SWAN follow-up (MPS baseline, 1999–2000,  $n = 2694$ ). The SWAN-MPS was designed to evaluate multiple environmental chemicals measured in serum and urine, one class at a time as well as all chemicals as mixtures; participants who had sufficient volumes of both serum and urine were eligible. Women from Chicago ( $n = 368$ ) and Newark ( $n = 278$ ) were not eligible because urine samples were not collected at these sites. Women with insufficient serum or urine samples were excluded ( $n = 648$ ), resulting in a base sample of 1400 women from four racial/ethnic groups (White, Black, Chinese and Japanese) for the SWAN-MPS. Women excluded due to insufficient serum/urine samples, compared with those included in the SWAN-MPS, were more likely to be obese, former or current smokers, and physically inactive, and to have lower education levels (electronic supplementary material [ESM] Table 1). For



**Fig. 1** Structures of the linear isomers of PFOA and PFOS (n-PFOA and n-PFOS, respectively). Caprylic acid, a fatty acid with eight carbons, is included for comparison

the current analysis, we excluded 82 women with prevalent diabetes at SWAN-MPS baseline and 81 women who had missing data for the key covariates, yielding a final analytical sample of 1237 women followed from 1999/2000 through 2017 (ESM Fig. 1).

**Incident diabetes** At each follow-up visit, women with incident diabetes were identified by the presence of one or more of the following conditions: (1) use of a glucose-lowering medication at any visit; (2) fasting glucose  $\geq 7$  mmol/l on two consecutive visits while not on steroids; and (3) any two visits with self-reported diabetes and at least one visit with fasting blood glucose  $\geq 7$  mmol/l. The date of the SWAN visit was used instead of the actual date of diagnosis. See ESM [Methods](#) for further details of incident diabetes ascertainment. Fasting serum glucose level was measured by the hexokinase method (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). The type of diabetes (i.e. type 1 or type 2) was not determined but most of the incident cases of diabetes at this life stage can be assumed to be type 2.

**Serum PFAS concentrations** Serum samples collected at SWAN-MPS baseline were sent to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) for PFAS concentration assessments. The laboratory's involvement did not constitute engagement in human studies. Online solid-phase extraction–HPLC–isotope dilution–tandem MS (SPE-HPLC-MS/MS) was used to quantify concentrations of 11 PFAS: linear PFOA (n-PFOA); sum of branched PFOA isomers (Sb-PFOA); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFUnDA); perfluorododecanoic acid (PFDoDA); perfluorohexane sulfonic acid (PFHxS); linear PFOS (n-PFOS); sum of perfluoromethylheptane sulfonic acid isomers (Sm-PFOS); 2-(*N*-methyl-perfluorooctane sulfonamido) acetic acid (MeFOSAA); and 2-(*N*-ethyl-perfluorooctane sulfonamido) acetic acid (EtFOSAA) [28]. Total PFOS concentration was computed as the sum of linear and branched PFOS. The analytic methods and quality control procedures have been described previously [29, 30]. The limit of detection (LOD) for all analytes was 0.1 ng/ml. We did not include Sb-PFOA, PFDA, PFUnDA or PFDoDA in data analyses due to low detection rates (<50%). Detection rates of all included PFAS were >96% (ESM Table 2). We also computed the sum of n-PFOA, PFNA, PFHxS and total PFOS because the recent risk assessment of the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain was based on the sum of these four common PFAS [31]. Participants with PFAS concentrations below LODs were assigned values equal to  $\text{LOD}/\sqrt{2}$ . The CV of low- and high-concentration quality controls ranged from 6% to 12%, depending on the analyte.

**Other covariates** Sociodemographic variables including age, race/ethnicity (White, Black, Chinese, Japanese) and educational attainment ( $\leq$ high school, some college,  $\geq$ college degree) were ascertained through a self-administered questionnaire at baseline. At each follow-up visit, cigarette smoking (never, former, current smoker), alcohol consumption (<1 drink/month,  $\geq 1$  drink/month and <2 drinks/week,  $\geq 2$  drinks/week), physical activity, total energy intake, parity (nulliparous, 1 or 2 births, 3+ births) and menopausal status (premenopausal, postmenopausal, unknown due to hormone therapy) were obtained from standardised interviews. Physical activity (score from 3 to 15) was assessed using a modified Kaiser Physical Activity Survey to determine the physical activity level in active living, household/caregiving and sports/exercise during the past 12 months. Total energy intake was calculated by summing the production of each food's consumption frequency from a detailed semi-quantitative food frequency questionnaire by the corresponding energy content. BMI was calculated as weight (kg) divided by squared height (m). We did not consider time-varying BMI and menopausal status given the evidence that these variables may be affected by PFAS and thus introduce overadjustment bias [32, 33].

**Statistical analysis** Univariate statistics were calculated and compared by incident diabetes using  $\chi^2$  test for categorical variables and Wilcoxon rank-sum test for continuous variables. Cox proportional hazards models were used to calculate HRs and 95% CIs for incident diabetes associated with each PFAS concentration. We used age as the time scale, and participants contributed survival time from the SWAN-MPS baseline to the date of the first diabetes diagnosis for incident cases or the last follow-up visit for non-cases. To capture potential non-linear associations as well as to ensure enough cases of diabetes in each exposure group, serum PFAS concentrations were categorised into tertiles. HRs (95% CIs) of diabetes were calculated comparing the highest/middle tertile with the lowest tertile of PFAS concentrations (reference group). A linear trend of the association across the tertiles was tested by including PFAS tertiles as a continuous variable. We also examined the associations using  $\log_2$ -transformed continuous PFAS concentrations. HRs were interpreted as effect per doubling of PFAS concentration. Potential confounders were chosen based on prior knowledge [34] and adjusted progressively. The base model adjusted for race/ethnicity and study sites. The full model additionally adjusted for education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline) and BMI (baseline). Smoking status, alcohol consumption, physical activity and total energy intake were time-varying. The proportional hazards assumption was checked using the scaled Schoenfeld residuals, and no significant violations were found. As sensitivity analyses, we evaluated the impact of additional adjustment for meat

consumption and parity as well as time-on-study (time since baseline) with adjustment for age as a covariate instead of age as the time scale. We also computed race-specific associations by including interactions between each PFAS and either Black or Asian women compared with White women.

We recognised that selective participation in the SWAN-MPS might have biased the associations between PFAS and incident diabetes. We expected that estimates of the PFAS–diabetes association would be weaker than the true causal effects because women who might be more susceptible to metabolic effects of PFAS were more likely to have dropped out or developed diabetes before the baseline of the SWAN-MPS. Women excluded due to insufficient biospecimens were less educated and had higher BMI (ESM Table 1); these characteristics are related to high PFAS exposure [29] and higher risk of diabetes [34]. Therefore, restriction to those who participated in the SWAN-MPS could lead to underestimation. To reduce this potential bias, we used inverse probability weighting (IPW) to develop a non-response weight to create a pseudo population representing the women who were at risk of incident diabetes at the time of serum PFAS measurements in the original SWAN cohort. See ESM Methods for further details illustrating the construction of IPW.

We used the quantile-based g-computation to investigate the joint effects of PFAS mixtures on incident diabetes [35]. Serum concentrations of all seven PFAS were included in the same quantile-based g-computation model, and the joint effect was evaluated through estimating the HR of diabetes for a one quantile simultaneous increase in all PFAS in this specified mixture. For the current analysis, the quantile-based g-computation was implemented by categorising all PFAS into tertiles. Each PFAS component was assigned a weight corresponding to the proportion of the joint effect of the mixture attributed to that component. When coefficients of PFAS components were not in the same direction, two sets of weights that yielded the proportion of the positive (or negative) ‘partial effect’ of all PFAS components with positive (or negative) coefficients were calculated (ESM Fig. 2). The same covariates used in the full models above were used in the quantile-based g-computation model. The R package ‘qgcomp’ (version 2.8.5) was used [35].

All statistical analyses were conducted using SAS (version 9.4 SAS Institute, Cary, NC, USA) and R (version 4.0.5; R Foundation for Statistical Computing). Statistical significance was defined at  $\alpha < 0.05$ .

## Results

At SWAN-MPS baseline, the median age was 49.4 years (IQR 47.4–51.5) and the proportions of each racial/ethnic group were 51.7% for White, 19.2% for Black, 13.3% for Chinese, and 15.8% for Japanese (Table 1). Among 1237

participants at risk for diabetes at SWAN-MPS baseline, 102 developed incident diabetes during 17,005 person-years of follow-up, an incidence of 6 per 1000 person-years. Compared with women who remained free of diabetes throughout follow-up, those who developed diabetes were more likely to be Black, from southeast Michigan, less educated and less physically active, to have a higher energy consumption and to have higher BMI at baseline. Women with incident diabetes had higher serum concentrations of total PFOS, n-PFOS, Sm-PFOS, MeFOSAA and EtFOSAA than those without incident diabetes. Women with higher concentrations of the sum of n-PFOA, PFNA, PFHxS and total PFOS were more likely to be Black, from southeast Michigan, former or current smokers and postmenopausal, and to have higher BMI (ESM Table 3).

Associations between serum PFAS concentrations and incident diabetes are presented in Table 2. After adjusting for race/ethnicity, study site, education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status and BMI (full model), the HRs (95% CIs) for the highest vs lowest tertile were 1.67 (1.21, 2.31) for n-PFOA ( $p_{\text{trend}} = 0.001$ ), 1.58 (1.13, 2.21) for PFHxS ( $p_{\text{trend}} = 0.003$ ), 1.36 (0.97, 1.90) for Sm-PFOS ( $p_{\text{trend}} = 0.05$ ), 1.85 (1.28, 2.67) for MeFOSAA ( $p_{\text{trend}} = 0.0004$ ), and 1.64 (1.17, 2.31) for the sum of four common PFAS (n-PFOA, PFNA, PFHxS and total PFOS) ( $p_{\text{trend}} = 0.002$ ). Statistically significant positive associations were also observed for total PFOS, n-PFOS and MeFOSAA when they were fit as continuous variables (log<sub>2</sub>-transformed). Fully adjusted HRs (95% CIs) for diabetes associated with each doubling of serum concentration were 1.22 (1.05, 1.43) for total PFOS, 1.22 (1.04, 1.42) for n-PFOS and 1.23 (1.07, 1.42) for MeFOSAA. The results remained essentially unchanged when time-on-study instead of age was used as the time scale except PFNA now reached statistical significance (HR 1.42 [95% CI 1.00, 2.00]) for highest vs lowest tertile ( $p_{\text{trend}} = 0.05$ ) (ESM Table 4). Additional adjustment for meat consumption or parity did not change the results (ESM Table 5). As expected, the results were attenuated when the models did not account for potential selection bias (i.e. without IPW) (ESM Table 6). The associations between PFAS and diabetes were generally larger and statistically significant only among White women but no associations were found among Black or Asian women except for MeFOSAA among Black women (ESM Table 7).

In the quantile-based g-computation evaluating the overall joint effects of PFAS mixtures (Fig. 2), increasing all seven PFAS serum concentrations by one tertile was associated with an elevated incidence of diabetes (HR 1.62 [95% CI 1.06, 2.49]) in the fully adjusted model. The HR comparing tertile 3 vs tertile 1 for all seven PFAS concentrations was 2.62 (95% CI 1.12, 6.20).

**Table 1** Baseline characteristics of study participants in the SWAN-MPS

Characteristic	Total population ( <i>n</i> =1237)	No diabetes ( <i>n</i> =1135)	Diabetes ( <i>n</i> =102)	<i>p</i> value <sup>a</sup>
Age, years	49.4 (47.4–51.5)	49.5 (47.4–51.6)	50.0 (47.7–52.2)	0.11
BMI, kg/m <sup>2</sup>	25.6 (22.3–30.7)	25.3 (22.2–30.0)	31.6 (26.9–37.3)	<0.0001
Physical activity score	7.9 (6.7–9.1)	8.0 (6.7–9.1)	7.4 (6.6–8.5)	0.04
Total energy intake, kJ	7000 (5569–8945)	6950 (5540–8832)	8163 (6176–10,209)	0.0003
Race/ethnicity, <i>n</i> (%)				0.0005
White	640 (51.7)	601 (53.0)	39 (38.2)	
Black	237 (19.2)	202 (17.8)	35 (34.1)	
Chinese	164 (13.3)	150 (13.2)	14 (13.7)	
Japanese	196 (15.8)	182 (16.0)	14 (13.7)	
Study site, <i>n</i> (%)				<0.0001
Southeast Michigan	205 (16.6)	172 (15.2)	33 (32.4)	
Boston	194 (15.7)	187 (16.5)	7 (6.9)	
Oakland	283 (22.9)	263 (23.2)	20 (19.6)	
Los Angeles	346 (28.0)	327 (28.8)	19 (18.6)	
Pittsburgh	209 (16.9)	186 (16.4)	23 (22.6)	
Education, <i>n</i> (%)				0.01
High school or less	209 (16.9)	189 (16.7)	20 (19.6)	
Some college	386 (31.2)	343 (30.2)	43 (42.2)	
College and above	642 (51.9)	603 (53.1)	39 (38.2)	
Smoking status, <i>n</i> (%)				0.09
Never	795 (64.3)	737 (64.9)	58 (56.9)	
Former	328 (26.5)	299 (26.3)	29 (28.4)	
Current	114 (9.2)	99 (8.7)	15 (14.7)	
Alcohol consumption, <i>n</i> (%)				0.02
<1 drink/month	636 (51.4)	573 (50.5)	63 (61.8)	
≥1 drink/month and <2 drinks/week	296 (23.9)	271 (23.9)	25 (24.5)	
≥2 drinks/week	305 (24.7)	291 (25.6)	14 (13.7)	
Menopausal status, <i>n</i> (%)				0.04
Premenopausal	860 (69.5)	796 (70.1)	64 (62.8)	
Postmenopausal	180 (14.6)	162 (14.3)	18 (17.6)	
Unknown <sup>b</sup>	197 (15.9)	177 (15.6)	20 (19.6)	
Serum PFAS concentration, ng/ml				
n-PFOA	4.1 (2.8–5.8)	4.0 (2.8–5.8)	4.9 (2.9–6.2)	0.32
PFNA	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.72
PFHxS	1.5 (1.0–2.3)	1.5 (1.0–2.3)	1.7 (1.1–2.8)	0.32
Total PFOS	24.2 (17.3–35.2)	23.9 (17.1–34.7)	28.2 (18.5–42.0)	0.01
n-PFOS	17.2 (12.2–24.6)	16.9 (12.2–24.0)	18.8 (13.4–28.6)	0.01
Sm-PFOS	7.2 (4.6–10.8)	7.0 (4.6–10.6)	8.6 (5.0–12.1)	0.03
MeFOSAA	1.4 (0.9–2.3)	1.4 (0.9–2.2)	2.0 (1.1–2.8)	0.003
EtFOSAA	1.2 (0.6–2.2)	1.1 (0.6–2.1)	1.4 (0.7–2.5)	0.03
Sum of n-PFOA, PFNA, PFHxS and total PFOS	31.4 (22.6–44.1)	31.0 (22.5–43.2)	36.7 (26.1–52.4)	0.01

Data are presented as median (IQR) or *n* (%)

<sup>a</sup>*p* value based on  $\chi^2$  test for categorical variables and Wilcoxon rank-sum test for continuous variables

<sup>b</sup>Menopausal status unknown due to hormone therapy or hysterectomy

**Table 2** HR (95% CI) of incident diabetes by tertiles of and per doubling in serum PFAS concentrations

PFAS	Tertile of PFAS concentrations			<i>p</i> value for trend	HR per doubling <sup>a</sup>	<i>p</i> value
	Tertile 1	Tertile 2	Tertile 3			
<b>n-PFOA</b>						
Range, ng/ml <sup>b</sup>	<3.2	3.3–5.0	5.1–56.5			
No. cases/person-years	29/5699	28/5646	45/5659			
Base model <sup>c</sup>	Ref	1.11 (0.78, 1.58)	1.61 (1.16, 2.23)	0.003	1.11 (0.95, 1.30)	0.19
Full model <sup>d</sup>	Ref	1.00 (0.70, 1.43)	1.67 (1.21, 2.31)	0.001	1.10 (0.94, 1.29)	0.24
<b>PFNA</b>						
Range, ng/ml <sup>b</sup>	<0.4	0.5–0.7	0.8–5.0			
No. cases/person-years	30/5256	40/6774	32/4975			
Base model <sup>c</sup>	Ref	1.13 (0.82, 1.55)	1.05 (0.75, 1.48)	0.80	1.02 (0.88, 1.18)	0.80
Full model <sup>d</sup>	Ref	1.26 (0.91, 1.73)	1.34 (0.95, 1.90)	0.10	1.11 (0.96, 1.28)	0.14
<b>PFHxS</b>						
Range, ng/ml <sup>b</sup>	<1.1	1.2–1.9	2.0–46.5			
No. cases/person-years	28/5708	29/5820	45/5478			
Base model <sup>c</sup>	Ref	0.90 (0.63, 1.29)	1.48 (1.07, 2.05)	0.008	1.04 (0.93, 1.16)	0.50
Full model <sup>d</sup>	Ref	0.90 (0.63, 1.28)	1.58 (1.13, 2.21)	0.003	1.07 (0.96, 1.20)	0.20
<b>Total PFOS</b>						
Range, ng/ml	2.0–19.6	19.7–30.2	30.3–376.0			
No. cases/person-years	27/5710	31/5704	44/5591			
Base model <sup>c</sup>	Ref	1.01 (0.71–1.43)	1.39 (1.01–1.93)	0.03	1.20 (1.04, 1.40)	0.01
Full model <sup>d</sup>	Ref	0.87 (0.61, 1.24)	1.25 (0.90, 1.74)	0.11	1.22 (1.05, 1.43)	0.01
<b>n-PFOS</b>						
Range, ng/ml	1.4–13.8	13.9–21.0	21.1–250.0			
No. cases/person-years	28/5757	28/5677	46/5570			
Base model <sup>c</sup>	Ref	0.91 (0.64, 1.29)	1.33 (0.97, 1.83)	0.05	1.19 (1.03, 1.38)	0.02
Full model <sup>d</sup>	Ref	0.83 (0.58, 1.19)	1.16 (0.84, 1.61)	0.28	1.22 (1.04, 1.42)	0.01
<b>Sm-PFOS</b>						
Range, ng/ml <sup>b</sup>	<5.3	5.4–9.1	9.2–126.0			
No. cases/person-years	28/5621	31/5880	43/5504			
Base model <sup>c</sup>	Ref	1.18 (0.84, 1.66)	1.51 (1.08, 2.11)	0.01	1.15 (1.01, 1.31)	0.04
Full model <sup>d</sup>	Ref	0.97 (0.68, 1.38)	1.36 (0.97, 1.90)	0.05	1.14 (0.99, 1.31)	0.06
<b>MeFOSAA</b>						
Range, ng/ml <sup>b</sup>	<1.0	1.1–1.9	2.0–11.5			
No. cases/person-years	22/5457	28/5975	52/5572			
Base model <sup>c</sup>	Ref	1.24 (0.84, 1.83)	1.96 (1.35, 2.84)	0.0001	1.23 (1.07, 1.41)	0.003
Full model <sup>d</sup>	Ref	1.21 (0.82, 1.79)	1.85 (1.28, 2.67)	0.0004	1.23 (1.07, 1.42)	0.004
<b>EtFOSAA</b>						
Range, ng/ml <sup>b</sup>	<0.7	0.8–1.6	1.7–112.5			
No. cases/person-years	27/5574	34/5859	41/5573			
Base model <sup>c</sup>	Ref	1.24 (0.89, 1.73)	1.20 (0.85, 1.70)	0.33	1.11 (1.01, 1.23)	0.03
Full model <sup>d</sup>	Ref	1.05 (0.75, 1.48)	0.91 (0.64, 1.28)	0.50	1.07 (0.97, 1.19)	0.19
<b>Sum of n-PFOA, PFNA, PFHxS, total PFOS</b>						
Range, ng/ml	2.2–25.5	25.6–38.7	38.8–431.3			
No. cases/person-years	24/5735	31/5686	47/5584			
Base model <sup>c</sup>	Ref	1.27 (0.89, 1.82)	1.75 (1.26, 2.45)	0.0008	1.20 (1.02, 1.40)	0.02
Full model <sup>d</sup>	Ref	1.06 (0.73, 1.52)	1.64 (1.17, 2.31)	0.002	1.22 (1.04, 1.44)	0.02

All models were constructed using Cox proportional hazards model

<sup>a</sup> Results based on when PFAS variables were fit as continuous variables (log<sub>2</sub>-transformed)

<sup>b</sup> Where serum PFAS concentration was below the LOD, the LOD is presented, rather than a range

<sup>c</sup> Base model: adjustment for race/ethnicity and study sites; age was used as the time scale

<sup>d</sup> Full model: adjustment as for base model with additional adjustment for education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline) and BMI (baseline)

## Discussion

This prospective cohort study supports the hypothesis that higher serum concentrations of n-PFOA, PFHxS, PFOS and MeFOSAA are associated with higher risk of incident diabetes. Combined exposure to seven PFAS was associated with an HR of 2.62 (95% CI 1.12, 6.20) when comparing the top vs the bottom tertile for all seven PFAS; this risk was greater than that seen with individual PFAS (HR range 1.36–1.85), suggesting a potential additive or synergistic effect of multiple PFAS on diabetes risk.

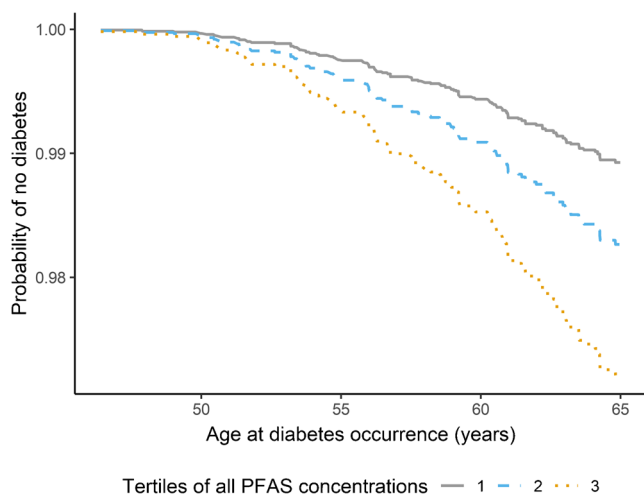
The large magnitude of the association between combined exposure to PFAS and incident diabetes from the mixture analysis (quantile-based g-computation) also suggests that PFAS may have substantial clinical impacts on diabetes risk. The HR of 2.62 was roughly equivalent to the magnitude of the HR for overweight individuals ( $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ ) vs those with  $\text{BMI} < 25 \text{ kg/m}^2$  (HR 2.89) observed in our study (ESM Table 8) and the pooled RR (2.99) from a meta-analysis [36], and even greater than that for current smokers vs never smokers (HR 2.30) in our population and the pooled RR (1.57) from a meta-analysis [37]. Given the widespread exposure to PFAS in the general population, the expected benefit of reducing exposure to these ubiquitous chemicals might be considerable.

Our findings are in line with those of the Nurses' Health Study-II (NHS-II) nested case-control study with 1586 women aged  $45.3 \pm 4.4$  years (793 case-control pairs) [21]. They found that fully adjusted ORs (95% CIs) for incident

diabetes comparing the top with the bottom tertile of plasma concentrations were 1.54 (1.04, 2.28) for PFOA and 1.62 (1.09, 2.41) for PFOS. The corresponding HRs (95% CIs) in our study were 1.67 (1.21, 2.31) for PFOA and 1.25 (0.90, 1.74) for PFOS. When  $\log_2$ -transformed PFAS were modelled, ORs (95% CIs) were 1.29 (1.07, 1.56) for PFOA and 1.20 (0.97, 1.47) for PFOS (recalculated using the reported ORs for a 1-SD increase in  $\log_{10}$ -transformed PFAS) in the NHS-II. The corresponding HRs (95% CIs) in our study were 1.10 (0.94, 1.29) for PFOA and 1.22 (1.05, 1.43) for PFOS. This suggests that the associations between the two studies are comparable depending on the shape of the dose-response associations. We observed a significant HR of 1.58 (95% CI 1.13, 2.21) (tertile 3 vs tertile 1) for PFHxS, whereas the NHS-II found a non-significant association (OR 1.28 [95% CI 0.86, 1.86]). PFNA was not significantly associated with incident diabetes in either study.

Another prospective study of 957 adults from the Diabetes Prevention Program (DPP) trial and Diabetes Prevention Program Outcomes Study (DPPPOS) (aged  $\geq 25$  years, 65.3% female sex, PFAS concentrations from plasma collected at baseline [1996–1999] and the second year of follow-up) found that a doubling of branched PFOA was associated with an HR of 1.14 (95% CI 1.04, 1.25) in the placebo group but no association was observed in the lifestyle intervention group [22]. Other PFAS were not associated with incident diabetes in either group.

Two other prospective studies failed to detect significant associations between PFAS and incident diabetes [23, 24]. A large cohort study of 32,254 community residents and workers (aged 20–110 years; 53.8% female sex; annual retrospective PFOA serum concentrations estimated from 1951 or participant's birth year through 2011) who were exposed to high levels of PFOA via contaminated drinking water in the Mid-Ohio Valley, West Virginia found no association between serum PFOA and incident diabetes [24]. A nested case-control study within the Swedish prospective population-based Västerbotten Intervention Programme cohort (124 case-control pairs; mean age 46 years; 42% female sex; PFAS concentrations from plasma collected in 1990–2003) found non-significant inverse associations [23]. It is not clear why our findings are similar to those of the NHS-II but different from these other studies. Similar population characteristics such as age (midlife) and sex (women), and exposure assessment timing (blood collected around the peak exposure before the population concentrations of PFOS and PFOA started to drop) may explain those discrepancies. If true, this may imply that midlife women may be more susceptible to PFAS-related diabetes risk. Although evidence of sex-dependent associations between PFAS and diabetes in human populations is lacking, a recent study in mice found that female mice had greater hepatic responses to PFOA exposure



**Fig. 2** Adjusted survival curves for incident diabetes by tertile of serum concentrations of PFAS mixtures from quantile-based g-computation, after adjusting for race/ethnicity, study site, education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline level) and BMI (baseline level). HR 1.62 (95% CI 1.06, 2.49) for increasing all seven PFAS concentrations by one tertile. HR 2.62 (95% CI 1.12, 6.20) for comparing tertile 3 (dotted yellow line) vs tertile 1 (solid grey line) for all seven PFAS concentrations



than male mice [38]. Potential effect modification by age and sex in the association between PFAS and incident diabetes needs to be assessed.

Underlying biological mechanisms of PFAS-induced diabetes risk are not fully understood. PFAS are structurally analogous to fatty acids, well-known endogenous ligands of PPAR $\alpha$  and PPAR $\gamma$ . Activation of PPARs by PFOA, PFOS and other substances has been observed in rodents as well as in humans [9]. Human-relevant doses of PFAS have been associated with promotion of adipocyte proliferation and differentiation, which play a pivotal role in disturbed lipid and glucose homeostasis and inflammatory responses [10, 11]. However, activation of PPAR $\alpha$  by PFAS, demonstrated in rodent studies to be the primary underlying mechanism, has been questioned in humans because the expression PPAR $\alpha$  is low in human liver [39]. Additionally, the fact that exposure to PFOA or PFOS in PPAR $\alpha$ -null mice increased hepatic lipid accumulation suggests the involvement of PPAR $\alpha$ -independent pathways [39]. Other nuclear receptors such as constitutive androstane receptor and pregnane X receptor, known to alter glucose and lipid metabolisms [40], can be activated by PFAS [39]. Inhibition of the phosphorylation and activation of Akt upon PFOS exposure is another potential mechanism of PFOS-induced insulin resistance [41]. PFOS may also affect glucose homeostasis by interfering with the glucose-lowering effects of metformin and energy restriction [42].

The present study has numerous strengths. First, it evaluated incident diabetes and confounders prospectively for up to 18 years. The prospective design prevented potential reverse causality that could have happened in cross-sectional or prevalent case–control study designs because blood concentrations of PFAS can be influenced by reduced kidney function, which is common in diabetic individuals [19, 20]. Second, our study population included racially/ethnically diverse women, thus increasing the generalisability of our findings. Third, to the best of our knowledge, this is the first study to evaluate the joint effect of PFAS mixtures on diabetes risk. Using the quantile-based g-computation approach [35], we found that the strength of the association for exposure to a combination of PFAS was greater than those for individual compounds.

Several limitations should also be considered. First, we cannot exclude the possibility that the observed associations are due to residual confounding. One potential source of confounding relates to bile acids when exposure to PFAS is assessed as serum concentrations [43]. PFAS are excreted in bile but most PFAS excreted into bile are reabsorbed in the intestine, in turn influencing serum PFAS concentrations. Bile acids play a role in glucose metabolism and insulin signalling through receptor-dependent and independent mechanisms [44]. Therefore, variability in the intestinal reabsorption of both PFAS and bile acids may confound the association between serum concentrations of PFAS and bile acid-

dependent health endpoints including diabetes. Second, although we claim that our racial/ethnic diverse female population is a strength of our study, our findings may not be generalisable to male sex, other ages and other ethnicities. Third, while long-chain PFAS have long elimination half-lives, single measurements assessed at baseline may have introduced exposure misclassification in later follow-up visits. However, the potential impact of such bias may be minimal given our observations of high intraclass correlations of repeated measured PFAS serum concentrations over 11 years [30].

In conclusion, this prospective cohort study supports the hypothesis that exposure to PFAS, individually and as mixtures, may increase the risk of incident diabetes in midlife women. Assuming that these results are applicable to men as well as to all ages, locations and races/ethnicities, if serum concentrations of total PFAS were reduced to the fifth percentile of the SWAN participants (15.3 ng/ml), the population attributable fraction for incident diabetes is approximately 25% for total PFAS (see [ESM Methods](#) for further details of the population attributable fraction calculation). Given that 1.5 million Americans are newly diagnosed with diabetes each year in the USA [45], approximately 370,000 new cases of diabetes annually in the USA are attributable to PFAS exposure. Our findings suggest that PFAS may be an important risk factor for diabetes that has a substantial public health impact. Despite the population-wide reduction in serum concentrations of PFOS and PFOA [46], almost all people are still exposed to these known ‘forever chemicals’ as well as innumerable alternatives and substitutes (e.g. short-chain PFAS) through drinking water, foods, air and consumer products including cosmetics [47]. Some residents living near industrial sites, military bases and waste-water treatment plants are exposed to substantially higher levels of PFAS [48] and may be at higher risk of developing diabetes. Reduced exposure to these ‘forever and everywhere chemicals’ even before entering midlife may be a key preventative approach to lowering the risk of diabetes. Policy changes around drinking water and consumer products could prevent population-wide exposure. Recent literature suggests that regulations that focus on a few specific PFAS may be ineffective and therefore persistent PFAS may need to be regulated as a class [49]. It is also important for clinicians to be aware of PFAS as unrecognised risk factors for diabetes and to be prepared to counsel patients in terms of sources of exposure and potential health effects [50].

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**Data availability** SWAN provides access to public-use datasets that include data from SWAN screening, the baseline visit and follow-up visits (<https://agingresearchbiobank.nia.nih.gov/>). To preserve participant confidentiality, some, but not all, of the data used for this manuscript are contained in the public-use datasets. A link to the public-use datasets is also located on the SWAN website: <http://www.swanstudy.org/swan-research/data-access/>. Investigators who require assistance accessing the public use dataset may contact the SWAN Coordinating Center at the following e-mail address: [swanaccess@edc.pitt.edu](mailto:swanaccess@edc.pitt.edu).

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critically revised the manuscript. CAKG, WHH, BM, AMC and SDH were involved in the design of the analysis plan, contributed to interpretation of the data, and critically revised the manuscript. All authors read and approved the final version of the paper. SKP is the guarantor of this work and had full access to all the data in the study and takes responsibility for the contents of the manuscript.

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