**Electronic Supplementary Material (ESM)**

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

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**ESM Methods**

***Incident diabetes ascertainment***

We used conservative criteria for incident diabetes to minimize outcome misclassification. 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 an anti-diabetic medication at any visit; 2) fasting glucose ≥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 ≥7 mmol/L. The date of SWAN visit instead of actual date of diagnosis was used. The SWAN visit at which diabetes may have developed among women who used anti-diabetic medication was defined as the first visit with serum glucose ≥7 mmol/L before first use of anti-diabetic medication; otherwise, the first visit with self-reported diabetes before first use of anti-diabetic medication; otherwise, the first visit at which the participant reported use of anti-diabetic medication. Among women who did not use anti-diabetic medication, the SWAN visit at which diabetes may have developed was defined as the first visit with serum glucose ≥7 mmol/L while not on steroids.

***Inverse probability weighting***

Selection bias may exist, as selection into SWAN MPS were probably affected by PFAS, their related diabetes risk factors, or potential confounders before or at the time of enrollment. In addition, selective loss to follow-up or other forms of attrition that occur after PFAS measurements may also bias estimates of associations between PFAS and diabetes if continuation in the follow-up is influenced by PFAS exposures and risk factors of diabetes. We addressed these two types of bias by using inverse probability weighting (IPW).

We used Repository samples available from the third SWAN follow-up visit (visit 03, 1999-2000) for PFAS measurements in our analysis. Women enrolled in SWAN were between

42 to 52 years at the SWAN baseline (visit 00, 1996-1997), which marked a time of increased risk for diabetes (1). Some of women who were at high risk of diabetes at the SWAN baseline have been censored before visit 03. Thus, participants susceptible to developing diabetes at the time of PFAS measurements were possibly different from the source population. On the other hand, at visit 03, only a subpopulation with 1,400 SWAN participants, but not all participants remained in the cohort had urine samples stored in the SWAN Biorepository assayed for PFAS concentrations. In this way, the analysis based on these 1,400 participants is likely to be susceptible to bias attributable to the selective participation in the substudy. IPW was used to alleviate the potential bias resulting from the selection into the SWAN multi-pollutant substudy (2). IPW uses information available for participants with and without PFAS measurements to weight observations from participants with PFAS measurements, so that the weighted subpopulation is representative of all SWAN participants in the original cohort who were continuing in the cohort and were free of diabetes at the time of PFAS measurements (visit 03). Probability of continuation in the follow-up study up to visit 03 and probability of selection into the substudy given that participants were not censored at visit 03 was modeled separately. We estimated the probability of continuing in the study up to visit 03 by using pooled logistic regression, conditional on covariates including age, race/ethnicity, study site, education level, marital status, husband's employment status, smoking, menopausal status, self-rated health, and diagnose of heart attack or angina, and on being uncensored at the previous visit. The reciprocal of this cumulative probability ($W_1$) is the weight of remaining free of diabetes and in the study at visit 03. For the probability of selection into the substudy given that participants were not censored at visit 03, we used a single logistic regression model to predict the probability, with age, study site, education level, smoking, menopausal status, total cholesterol level, low-density lipoprotein cholesterol level, triglyceride level, and hypertension included in the model. The reciprocal of this probability ($W_2$) is the weight of being selected into the substudy at visit 03.

Finally, we calculated a combined weight $W_{substudy} = W_1 \times W_2$, as the inverse of the probability of the conjunction of these two events.

We hypothesized that women with higher concentrations of PFAS would experience a higher risk of diabetes during follow-up after PFAS measurements. However, given the toxicity of PFAS, those with high concentrations who remained in the cohort might have other beneficial characteristics (healthier) that protected them from developing diabetes. This is because the risk factors for diabetes, especially those health conditions, predict the censoring or attrition after the PFAS measurements. In this way, the selection induces an association between PFAS and diabetes, even if there is no true effect. Similar to the strategy we used to address selective participation, IPW was used to reduce potential bias resulting from the selective attrition. The intuition behind these weights is that participants with characteristics similar to the observations missing due to attrition are upweighted to represent their original contribution and their missing contributions. We modeled and estimated the probability of continuing in the study after visit 03 by using pooled logistic regression, conditional on covariates including age, study site, SWAN visit number, household income, smoking, use of the hormone, self-rated health, BMI (linear and quadratic terms), and waist circumference (linear and quadratic terms), and on being uncensored at the previous visit. The reciprocal of this cumulative probability of continuing is the non-stabilized weight ($W_{atrrition}$). And the weight was applied at the level of observations within individuals.

We calculated the total $W = W_{substudy} \times W_{atrrition}$ for each participant in the PFAS-diabetes analysis as the inverse of the probability of being selected into the SWAN multi-pollutant substudy from the original SWAN cohort and of being uncensored up to a given study visit after PFAS measurements. To note, including covariates in the calculation of the weight is not sufficient to control for confounding when evaluating associations between PFAS and

diabetes incidence. As such, the potential confounders were adjusted as covariates in the Cox proportional hazards model in our primary analysis (2,3).

***Population Attributable Fraction***

We computed population attributable fraction (PAF) using the approach used in the disease burden for continuous risk factors (4). PAF in this study indicates the proportional reduction in new incident diabetes that would occur if exposure to PFAS in the population were reduced to the counterfactual of theoretical-minimum-risk exposure distribution. Because there are no known minimum risk exposure distributions for serum PFAS concentrations, we used the $5^{th}$ percentiles of each PFAS concentration in our population as the theoretical-minimum-risk exposure distributions. We computed total PFAS as the sum of individual PFAS concentrations and used the $5^{th}$ percentile as the theoretical-minimum-risk exposure distribution. Relative risks used to compute PAFs were based on fully adjusted HRs for log-2 transformed PFAS. The numbers of incident diabetes cases for each PFAS and PFAS mixture that would have been prevented annually in the US were estimated based on 1.5 million Americans with newly diagnosed diabetes per year (5).

**References**


1. Kim C. Does menopause increase diabetes risk? Strategies for diabetes prevention in midlife women. Womens Health. 2012;8(2):155–67.
2. Hernán MA, Hernández-Díaz S, Robins JM. A Structural Approach to Selection Bias. Epidemiology. 2004 Sep;15(5):615–25.
3. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, et al. Accounting for Bias Due to Selective Attrition: the example of smoking and cognitive

decline. Epidemiology. 2012;23(1):119–28.

4. Vander Hoorn S, Ezzati M, Rodgers A, Lopez AD, Murray CJL. Chapter 25: Estimating attributable burden of disease from exposure and hazard data. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, editors. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors [Internet]. Geneva: World Health Organization; 2004. p. 2129–40. Available from: https://www.who.int/publications/cra/chapters/volume2/2129-2140.pdf

5. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2020 [Internet]. Atlanta, GA; 2020. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

**ESM Table 1**. Characteristics of study participants who were included vs. who were not included in the SWAN-MPS.

| | Not included in SWAN-MPS (n=648) | Included in SWAN-MPS (n=1400) | P-value[‡] |
|---|---|---|---|
| Age (years)[*] | 49.3 (2.7) | 49.5 (2.6) | 0.12 |
| Body mass index (kg/m$^2$)[*] | 29.3 (7.6) | 27.9 (0.2) | 0.0001 |
| Physical activity score[*] | 7.6 (1.7) | 7.8 (1.8) | 0.001 |
| Race/ethnicity, n (%) | | | <0.0001 |
| White | 328 (50.6) | 708 (50.6) | |
| Black | 211 (32.6) | 308 (22.0) | |
| Chinese | 55 (8.5) | 177 (12.6) | |
| Japanese | 54 (8.3) | 207 (14.8) | |
| Study site, n (%) | | | <0.0001 |
| Michigan | 128 (19.8) | 257 (18.4) | |
| Boston | 159 (24.5) | 233 (16.6) | |
| Oakland | 103 (15.9) | 309 (22.1) | |
| Los Angeles | 96 (14.8) | 366 (26.1) | |
| Pittsburgh | 162 (25.0) | 235 (16.8) | |
| Education, n (%) | | | <0.0001 |
| High school or less | 155 (24.1) | 252 (18.1) | |
| Some College | 232 (36.0) | 448 (32.2) | |
| College and above | 257 (39.9) | 693 (49.8) | |
| Smoking status, n (%) | | | <0.0001 |
| Never | 307 (48.7) | 882 (63.1) | |
| Former | 216 (34.3) | 371 (26.5) | |
| Current | 107 (17.0) | 145 (10.4) | |
| Alcohol consumption, n (%) | | | 0.03 |
| <1/month | 311 (50.6) | 738 (52.9) | |
| ≥1/month and <2/week | 178 (28.9) | 328 (23.5) | |
| ≥2/week | 126 (20.5) | 328 (23.5) | |
| Menopausal status, n (%) | | | 0.25 |
| Pre-menopausal | 461 (71.1) | 994 (71.0) | |
| Post-menopausal | 80 (12.3) | 192 (13.7) | |
| Unknown[†] | 107 (16.5) | 214 (15.3) | |

[*]Mean (standard deviation).

[†]Menopausal status unknown due to hormone therapy or hysterectomy.

[‡]P-value based on Chi-squared test for categorical variables, t-test for age and physical activity score, and Wilcoxon rank-sum test for body mass index.

**ESM Table 2.** Distributions of PFAS concentrations (ng/mL).

| PFAS congeners | Detection (%) | Percentiles | | | | |
|---|---|---|---|---|---|---|
| | LOD = 0.1 | 10th | 25th | 50th | 75th | 90th |
| n-PFOA | 99.9 | 2.0 | 2.8 | 4.1 | 5.8 | 8.2 |
| PFNA | 96.9 | 0.3 | 0.4 | 0.6 | 0.8 | 1.0 |
| PFHxS | 99.6 | 0.6 | 1.0 | 1.5 | 2.3 | 4.3 |
| Total PFOS* | | 12.5 | 17.3 | 24.2 | 35.2 | 51.3 |
| n-PFOS | 100 | 8.9 | 12.2 | 17.2 | 24.6 | 36.0 |
| Sm-PFOS | 99.8 | 3.2 | 4.6 | 7.2 | 10.8 | 16.0 |
| MeFOSAA | 99.6 | 0.6 | 0.9 | 1.4 | 2.3 | 3.5 |
| EtFOSAA | 98.9 | 0.4 | 0.6 | 1.2 | 2.2 | 3.9 |

LOD, limit of detection; PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid.

*Total PFOS = n-PFOS + Sm-PFOS.

**ESM Table 3**. Baseline characteristics of study participants by tertiles of the sum of n-PFOA, PFNA, PFHxS, and total PFOS, the SWAN-MPS.

| | **Tertile 1 (n=416)** | **Tertile 2 (n=409)** | **Tertile 3 (n=412)** | **P-value‡** |
|---|---|---|---|---|
| Sum of n-PFOA, PFNA, PFHxS and total PFOS (ng/mL)* | 19.4 (15.5, 22.7) | 31.4 (28.0, 34.8) | 52.4 (44.1, 67.7) | |
| Age (years)* | 49.7 (47.5, 51.8) | 49.4 (47.3, 51.6) | 49.4 (47.4, 51.2) | 0.07 |
| Body mass index (kg/m$^2$)* | 24.5 (21.7, 28.6) | 25.4 (22.3, 30.8) | 27.1 (23.1, 32.6) | <0.0001 |
| Physical activity score* | 8.0 (6.7, 9.3) | 7.9 (6.6, 9.1) | 7.9 (6.8, 8.9) | 0.11 |
| Total energy intake (kcal)* | 1679 (1310, 2128) | 1671 (1341, 2139) | 1677 (1332, 2140) | 0.87 |
| Race/ethnicity, n (%) | | | | <0.0001 |
| White | 205 (49.3) | 213 (52.1) | 222 (53.9) | |
| Black | 59 (14.2) | 61 (14.9) | 117 (28.4) | |
| Chinese | 80 (19.2) | 58 (14.2) | 26 (6.3) | |
| Japanese | 72 (17.3) | 77 (18.8) | 47 (11.4) | |
| Study site, n (%) | | | | <0.0001 |
| Michigan | 48 (11.5) | 59 (14.4) | 98 (23.8) | |
| Boston | 71 (17.1) | 69 (16.9) | 54 (13.1) | |
| Oakland | 129 (31.0) | 95 (23.2) | 59 (14.3) | |
| Los Angeles | 114 (27.4) | 128 (31.3) | 104 (25.2) | |
| Pittsburgh | 54 (13.0) | 58 (14.2) | 97 (23.5) | |
| Education, n (%) | | | | 0.06 |
| High school or less | 73 (17.6) | 63 (15.4) | 73 (17.7) | |
| Some College | 110 (26.4) | 131 (32.0) | 145 (35.2) | |
| College and above | 233 (56.0) | 215 (52.6) | 194 (47.1) | |
| Smoking status, n (%) | | | | 0.01 |
| Never | 288 (69.2) | 266 (65.0) | 241 (58.5) | |
| Former | 101 (24.3) | 104 (25.4) | 123 (29.9) | |
| Current | 27 (6.5) | 39 (9.5) | 48 (11.6) | |
| Alcohol consumption, n (%) | | | | 0.28 |
| <1/month | 217 (52.2) | 207 (50.6) | 212 (51.5) | |
| ≥1/month and <2/week | 99 (23.8) | 88 (21.5) | 109 (26.5) | |
| ≥2/week | 100 (24.0) | 114 (27.9) | 91 (22.1) | |
| Menopausal status, n (%) | | | | 0.02 |
| Pre-menopausal | 309 (74.3) | 282 (69.0) | 269 (65.3) | |
| Post-menopausal | 47 (11.3) | 63 (15.3) | 70 (17.0) | |

| | | | | |
|---|---|---|---|---|
| Unknown[†] | 60 (14.4) | 64 (15.7) | 73 (17.7) | |

PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid.

[*]Median (interquartile range).

[†]Menopausal status unknown due to hormone therapy or hysterectomy.

[‡]P-value based on Chi-squared test for categorical variables, ANOVA for continuous variables.

**ESM Table 4.** Sensitivity analysis results [Hazard ratio (95% CI)] using time-on-study as the time scale instead of age.

| PFAS | Tertile of PFAS concentrations | | | P value for trend | Per doubling‡ | P value |
|---|---|---|---|---|---|---|
| | Tertile 1 | Tertile 2 | Tertile 3 | | | |
| **n-PFOA** | | | | | | |
| Range, ng/mL | <3.2 | 3.3–5.0 | 5.1–56.5 | | | |
| Original model* | Ref | 1.00 (0.70, 1.43) | 1.67 (1.21, 2.31) | 0.001 | 1.10 (0.94, 1.29) | 0.24 |
| Time-on-study as the time scale† | Ref | 0.99 (0.70, 1.42) | 1.68 (1.21, 2.32) | 0.001 | 1.12 (0.95, 1.31) | 0.17 |
| **PFNA** | | | | | | |
| Range, ng/mL | <0.4 | 0.5–0.7 | 0.8–5.0 | | | |
| Original model* | Ref | 1.26 (0.91, 1.73) | 1.34 (0.95, 1.90) | 0.10 | 1.11 (0.96, 1.28) | 0.14 |
| Time-on-study as the time scale† | Ref | 1.28 (0.93, 1.77) | 1.42 (1.00, 2.00) | 0.05 | 1.13 (0.98, 1.30) | 0.10 |
| **PFHxS** | | | | | | |
| Range, ng/mL | <1.1 | 1.2–1.9 | 2.0–46.5 | | | |
| Original model* | Ref | 0.90 (0.63, 1.28) | 1.58 (1.13, 2.21) | 0.003 | 1.07 (0.96, 1.20) | 0.20 |
| Time-on-study as the time scale† | Ref | 0.90 (0.63, 1.29) | 1.67 (1.19, 2.34) | 0.001 | 1.11 (0.99, 1.24) | 0.08 |
| **Total PFOS** | | | | | | |
| Range, ng/mL | 2.0–19.6 | 19.7–30.2 | 30.2–376.0 | | | |
| Original model* | Ref | 0.87 (0.61, 1.24) | 1.25 (0.90, 1.74) | 0.11 | 1.22 (1.05, 1.43) | 0.01 |
| Time-on-study as the time scale† | Ref | 0.89 (0.63, 1.27) | 1.25 (0.90, 1.74) | 0.12 | 1.21 (1.04, 1.41) | 0.02 |
| **n-PFOS** | | | | | | |
| Range, ng/mL | 1.4–13.8 | 13.9–21.0 | 21.1–250.0 | | | |
| Original model* | Ref | 0.83 (0.58, 1.19) | 1.16 (0.84, 1.61) | 0.28 | 1.22 (1.04, 1.42) | 0.01 |
| Time-on-study as the time scale† | Ref | 0.84 (0.58, 1.19) | 1.16 (0.83, 1.61) | 0.29 | 1.21 (1.04, 1.41) | 0.02 |
| **Sm-PFOS** | | | | | | |
| Range, ng/mL | <5.3 | 5.4–9.1 | 9.2–126.0 | | | |
| Original model* | Ref | 0.97 (0.68, 1.38) | 1.36 (0.97, 1.90) | 0.05 | 1.14 (0.99, 1.31) | 0.06 |
| Time-on-study as the time scale† | Ref | 0.97 (0.68, 1.39) | 1.34 (0.96, 1.88) | 0.06 | 1.13 (0.99, 1.30) | 0.08 |
| **MeFOSAA** | | | | | | |
| Range, ng/mL | <1.0 | 1.1–1.9 | 2.0–11.5 | | | |
| Original model* | Ref | 1.21 (0.82, 1.79) | 1.85 (1.28, 2.67) | 0.0004 | 1.23 (1.07, 1.42) | 0.004 |
| Time-on-study as the time scale† | Ref | 1.24 (0.84, 1.83) | 1.92 (1.32, 2.80) | 0.0002 | 1.24 (1.08, 1.43) | 0.003 |
| **EtFOSAA** | | | | | | |
| Range, ng/mL | <0.7 | 0.8–1.6 | 1.7–112.5 | | | |
| Original model* | Ref | 1.05 (0.75, 1.48) | 0.91 (0.64, 1.28) | 0.50 | 1.07 (0.97, 1.19) | 0.19 |
| Time-on-study as the time scale† | Ref | 0.99 (0.70, 1.40) | 0.86 (0.60, 1.22) | 0.34 | 1.07 (0.96, 1.19) | 0.23 |

All models were constructed by Cox proportional hazards model. PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid.
[*]Original model: age as the time scale with adjustment for race/ethnicity, study sites, education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline) and body mass index (baseline level).
[b†]Time-on-study was used as the time scale with adjustment for age as a covariate and all other covariates used in the original model.
[‡]Results based on when PFAS variables were fit as continuous variables (log2-transformed).

**ESM Table 5.** Sensitivity analysis results [Hazard ratio (95% CI)] with additional adjustment for meat consumption or parity.

| PFAS | Tertile of PFAS concentrations | | | P value for trend | Per doubling* | P value |
|---|---|---|---|---|---|---|
| | Tertile 1 | Tertile 2 | Tertile 3 | | | |
| **n-PFOA** | | | | | | |
| + meat consumption | Ref | 0.99 (0.69, 1.41) | 1.67 (1.20, 2.31) | 0.001 | 1.10 (0.94, 1.30) | 0.23 |
| + parity | Ref | 1.00 (0.70, 1.43) | 1.67 (1.21, 2.31) | 0.001 | 1.10 (0.94, 1.29) | 0.24 |
| **PFNA** | | | | | | |
| + meat consumption | Ref | 1.25 (0.91, 1.73) | 1.33 (0.94, 1.88) | 0.11 | 1.11 (0.96, 1.28) | 0.17 |
| + parity | Ref | 1.26 (0.91, 1.74) | 1.35 (0.95, 1.91) | 0.09 | 1.11 (0.97, 1.29) | 0.14 |
| **PFHxS** | | | | | | |
| + meat consumption | Ref | 0.90 (0.63, 1.28) | 1.57 (1.12, 2.20) | 0.004 | 1.07 (0.96, 1.20) | 0.21 |
| + parity | Ref | 0.90 (0.63, 1.29) | 1.58 (1.13, 2.21) | 0.003 | 1.07 (0.96, 1.20) | 0.20 |
| **Total PFOS** | | | | | | |
| + meat consumption | Ref | 0.86 (0.60, 1.22) | 1.26 (0.91, 1.76) | 0.10 | 1.23 (1.05, 1.44) | 0.01 |
| + parity | Ref | 0.87 (0.61, 1.24) | 1.25 (0.90, 1.74) | 0.11 | 1.22 (1.04, 1.43) | 0.01 |
| **n-PFOS** | | | | | | |
| + meat consumption | Ref | 0.82 (0.57, 1.17) | 1.16 (0.84, 1.61) | 0.27 | 1.22 (1.05, 1.43) | 0.01 |
| + parity | Ref | 0.83 (0.58, 1.19) | 1.16 (0.84, 1.61) | 0.28 | 1.22 (1.04, 1.42) | 0.01 |
| **Sm-PFOS** | | | | | | |
| + meat consumption | Ref | 0.95 (0.67, 1.36) | 1.37 (0.98, 1.92) | 0.04 | 1.15 (1.00, 1.32) | 0.05 |
| + parity | Ref | 0.97 (0.68, 1.38) | 1.36 (0.97, 1.90) | 0.05 | 1.14 (0.99, 1.31) | 0.06 |
| **MeFOSAA** | | | | | | |
| + meat consumption | Ref | 1.24 (0.84, 1.83) | 1.92 (1.32, 2.78) | 0.0002 | 1.24 (1.07, 1.42) | 0.003 |
| + parity | Ref | 1.21 (0.82, 1.79) | 1.85 (1.28, 2.67) | 0.0004 | 1.23 (1.07, 1.42) | 0.004 |
| **EtFOSAA** | | | | | | |
| + meat consumption | Ref | 1.06 (0.75, 1.49) | 0.92 (0.64, 1.30) | 0.54 | 1.08 (0.97, 1.20) | 0.16 |
| + parity | Ref | 1.05 (0.75, 1.48) | 0.91 (0.64, 1.29) | 0.50 | 1.07 (0.97, 1.19) | 0.19 |

All models were constructed using Cox proportional hazards model. PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acic; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; <LOD, below the limit of detection.

Original models: age as the time scale with adjustment for race/ethnicity, study sites, education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline) and body mass index (baseline level).

*Results based on when PFAS variables were fit as continuous variables (log2-transformed).

**ESM Table 6.** Sensitivity analysis results [Hazard ratio (95% CI)] without inverse probability weighting.

| PFAS | Tertile of PFAS concentrations | | | P value for trend | Per doubling[‡] | P value |
|---|---|---|---|---|---|---|
| | Tertile 1 | Tertile 2 | Tertile 3 | | | |
| **n-PFOA** | | | | | | |
| Range, ng/mL | <3.2 | 3.3–5.0 | 5.1–56.5 | | | |
| Base model[*] | Ref | 1.08 (0.63, 1.86) | 1.58 (0.95, 2.63) | 0.06 | 1.14 (0.89, 1.46) | 0.30 |
| Full model[†] | Ref | 0.94 (0.54, 1.64) | 1.54 (0.92, 2.56) | 0.07 | 1.11 (0.87, 1.43) | 0.40 |
| **PFNA** | | | | | | |
| Range, ng/mL | <0.4 | 0.5–0.7 | 0.8–5.0 | | | |
| Base model[*] | Ref | 1.00 (0.62, 1.62) | 0.98 (0.59, 1.64) | 0.95 | 0.98 (0.79, 1.23) | 0.89 |
| Full model[†] | Ref | 1.10 (0.68, 1.79) | 1.20 (0.71, 2.03) | 0.49 | 1.05 (0.84, 1.32) | 0.64 |
| **PFHxS** | | | | | | |
| Range, ng/mL | <1.1 | 1.2–1.9 | 2.0–46.5 | | | |
| Base model[*] | Ref | 1.02 (0.60, 1.72) | 1.48 (0.89, 2.44) | 0.11 | 1.02 (0.86, 1.22) | 0.78 |
| Full model[†] | Ref | 1.04 (0.61, 1.77) | 1.52 (0.90, 2.56) | 0.10 | 1.05 (0.88, 1.24) | 0.60 |
| **Total PFOS** | | | | | | |
| Range, ng/mL | 2.0–19.6 | 19.7–30.2 | 30.2–376.0 | | | |
| Base model[*] | Ref | 1.07 (0.64, 1.79) | 1.31 (0.79, 2.16) | 0.28 | 1.18 (0.94, 1.49) | 0.16 |
| Full model[†] | Ref | 0.91 (0.54, 1.55) | 1.13 (0.68, 1.89) | 0.59 | 1.17 (0.92, 1.48) | 0.21 |
| **n-PFOS** | | | | | | |
| Range, ng/mL | 1.4–13.8 | 13.9–21.0 | 21.1–250.0 | | | |
| Base model[*] | Ref | 0.95 (0.56, 1.61) | 1.29 (0.79, 2.11) | 0.29 | 1.16 (0.91, 1.46) | 0.23 |
| Full model[†] | Ref | 0.84 (0.49, 1.43) | 1.11 (0.67, 1.84) | 0.63 | 1.15 (0.90, 1.46) | 0.25 |
| **Sm-PFOS** | | | | | | |
| Range, ng/mL | <5.3 | 5.4–9.1 | 9.2–126.0 | | | |
| Base model[*] | Ref | 1.13 (0.67, 1.90) | 1.47 (0.89, 2.44) | 0.13 | 1.16 (0.95, 1.42) | 0.15 |
| Full model[†] | Ref | 0.89 (0.52, 1.53) | 1.28 (0.77, 2.15) | 0.27 | 1.13 (0.92, 1.40) | 0.26 |
| **MeFOSAA** | | | | | | |
| Range, ng/mL | <1.0 | 1.1–1.9 | 2.0–11.5 | | | |
| Base model[*] | Ref | 1.13 (0.64, 2.00) | 1.85 (1.07, 3.22) | 0.02 | 1.20 (0.97, 1.49) | 0.09 |
| Full model[†] | Ref | 1.08 (0.61, 1.93) | 1.64 (0.95, 2.84) | 0.06 | 1.17 (0.94, 1.44) | 0.17 |
| **EtFOSAA** | | | | | | |
| Range, ng/mL | <0.7 | 0.8–1.6 | 1.7–112.5 | | | |
| Base model[*] | Ref | 1.12 (0.67, 1.87) | 1.22 (0.73, 2.01) | 0.45 | 1.13 (0.97, 1.31) | 0.11 |
| Full model[b†] | Ref | 0.91 (0.53, 1.54) | 0.95 (0.56, 1.60) | 0.88 | 1.10 (0.93, 1.29) | 0.26 |

All models were constructed using Cox proportional hazards model. PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; <LOD, below the limit of detection.

*Base model: adjustment for race/ethnicity and study sites. Age was used as the time scale.

†Full model: additional adjustment for education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline), body mass index (baseline).

‡Results based on when PFAS variables were fit as continuous variables (log2-transformed).

**ESM Table 7.** Race-specific hazard ratio (HR) (95% confidence interval, 95% CI) of incident diabetes per doubling of serum PFAS concentrations.

| PFAS and race/ethnicity | HR (95% CI) per doubling of PFAS* | P for interaction‡ |
|---|---|---|
| **n-PFOA** | | |
| White | 1.41 (1.11, 1.79) | – |
| Black | 0.99 (0.77, 1.28) | 0.05 |
| Asian† | 0.76 (0.53, 1.08) | 0.004 |
| **PFNA** | | |
| White | 1.17 (0.91, 1.50) | – |
| Black | 1.06 (0.86, 1.30) | 0.55 |
| Asian† | 1.16 (0.85, 1.58) | 0.97 |
| **PFHxS** | | |
| White | 1.45 (1.22, 1.72) | – |
| Black | 0.87 (0.73, 1.04) | <0.0001 |
| Asian† | 0.92 (0.73, 1.16) | 0.002 |
| **Total PFOS** | | |
| White | 1.39 (1.10, 1.76) | – |
| Black | 1.14 (0.90, 1.44) | 0.25 |
| Asian† | 1.01 (0.69, 1.50) | 0.18 |
| **n-PFOS** | | |
| White | 1.34 (1.06, 1.69) | – |
| Black | 1.15 (0.91, 1.45) | 0.37 |
| Asian† | 1.08 (0.73, 1.60) | 0.36 |
| **Sm-PFOS** | | |
| White | 1.36 (1.08, 1.71) | – |
| Black | 1.08 (0.87, 1.33) | 0.15 |
| Asian† | 0.89 (0.66, 1.20) | 0.03 |
| **MeFOSAA** | | |
| White | 1.24 (1.00, 1.55) | – |
| Black | 1.70 (1.33, 2.18) | 0.06 |
| Asian† | 0.82 (0.63, 1.06) | 0.02 |
| **EtFOSAA** | | |
| White | 1.19 (1.01, 1.40) | – |
| Black | 1.09 (0.93, 1.28) | 0.46 |
| Asian† | 0.83 (0.65, 1.05) | 0.01 |

All models were constructed using Cox proportional hazards model. PFAS, per- and polyfluoroalkyl substances; n-PFOA, linear perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; n-PFOS, linear perfluorooctane sulfonic acid; Sm-PFOS, sum of perfluoromethylheptane sulfonic acid isomers; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; <LOD, below the limit of detection.

*Adjustment for study sites. education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline), body mass index (baseline), and parity. Interaction terms between race/ethnicity and PFAS were included in the models. Age was used as the time scale. Results based on when PFAS variables were fit as continuous variables (log2-transformed).

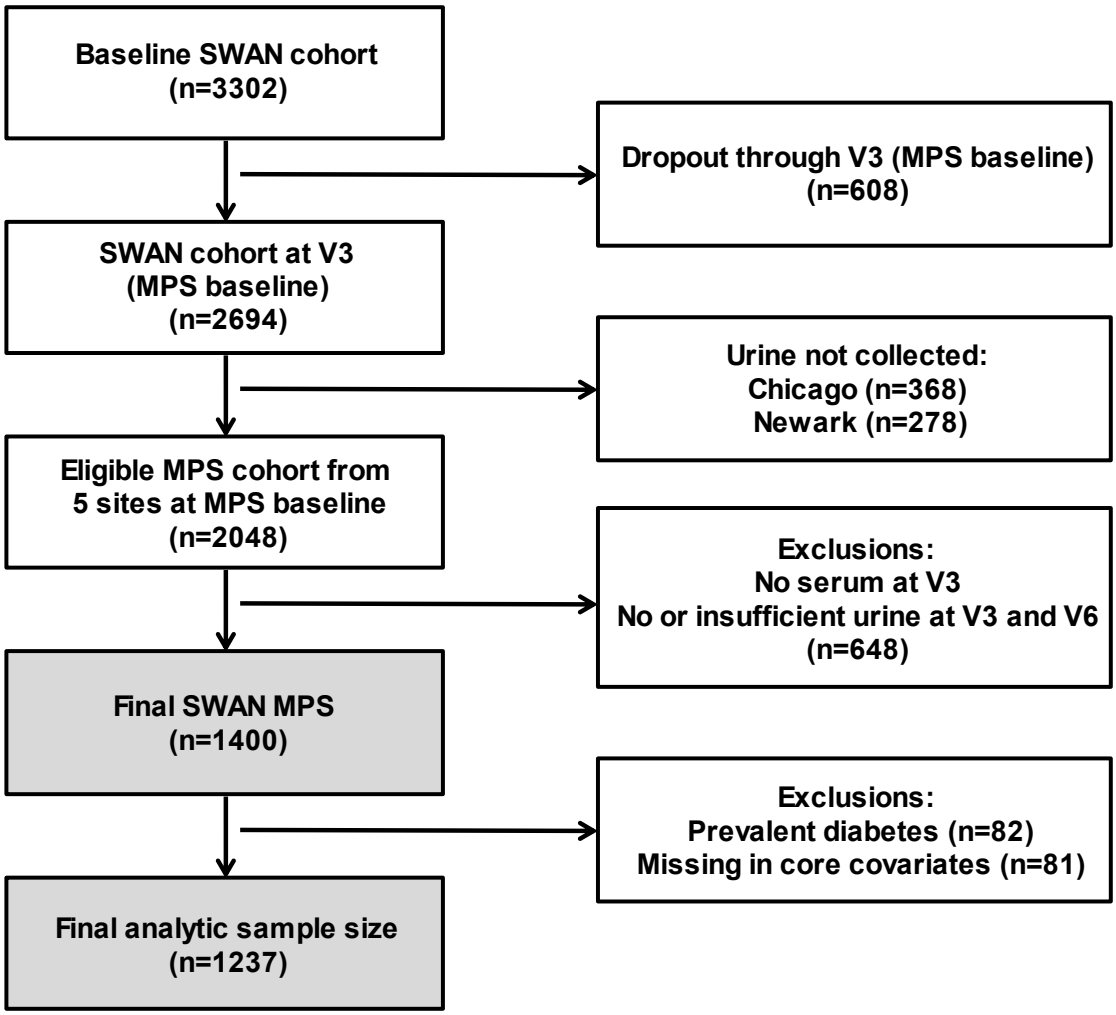
† Asian women including both Chinese and Japanese women.

‡ P-values from interaction terms between each PFAS and either Black women or Asian women compared with White women as the reference.

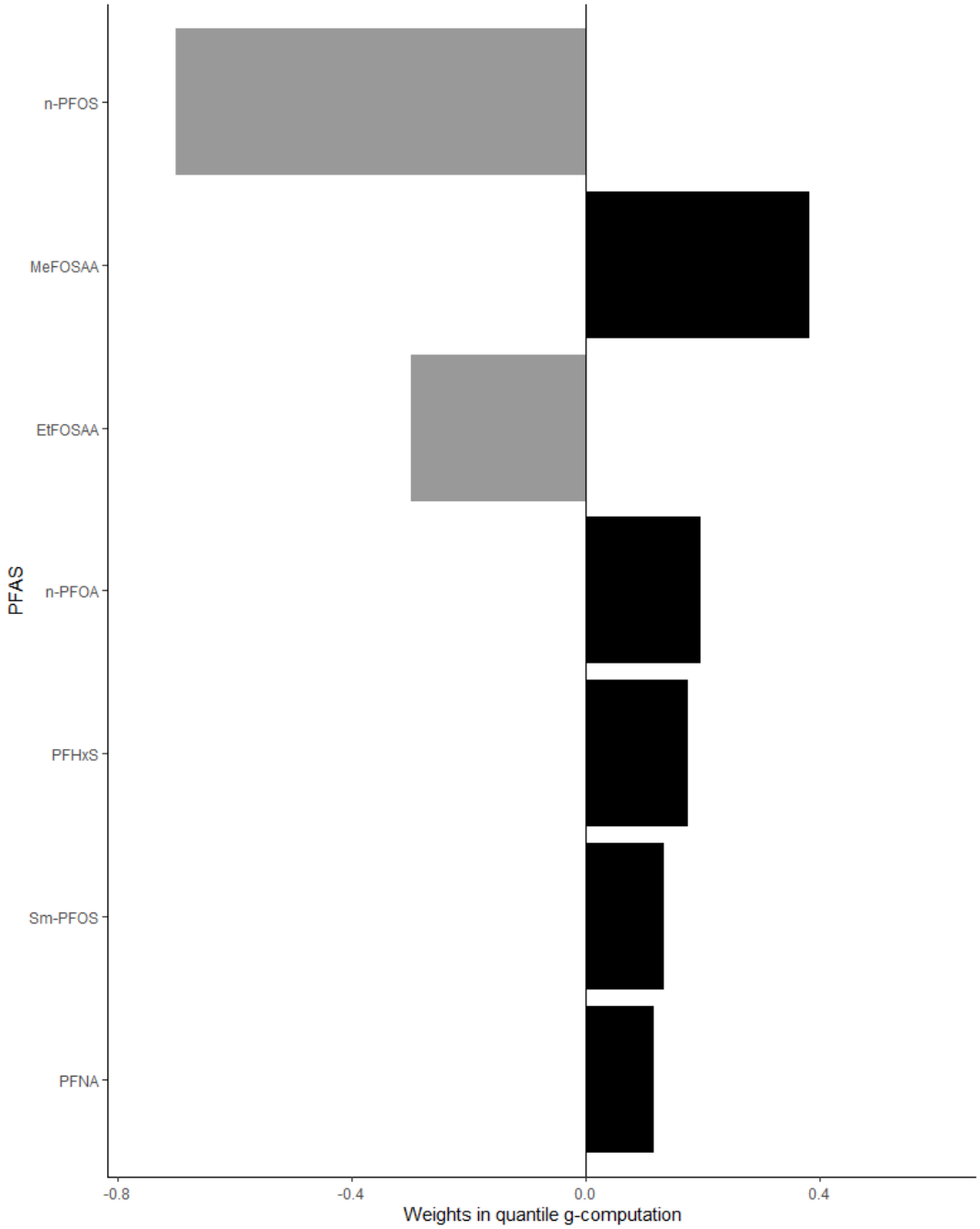
**ESM Table 8.** Hazard ratio (HR) (95% confidence interval, 95% CI) of incident diabetes with other risk factors in the Cox proportional hazards model.

| **Covariates** | **HR (95% CI)** |
|---|---|
| Black vs. White | 1.45 (1.05, 2.01) |
| Chinese vs. White | 3.53 (1.74, 7.15) |
| Japanese vs. White | 2.50 (1.11, 5.63) |
| Former smoker vs. never smoker | 1.37 (1.01, 1.85) |
| Current smoker vs never smoker | 2.30 (1.60, 3.30) |
| Overweight vs. normal weight | 2.89 (1.90, 4.39) |
| Obese vs. normal weight | 6.28 (4.18, 9.42) |

Model included race/ethnicity, study site, education, smoking status, alcohol consumption, physical activity score, total energy intake, menopausal status (baseline), categorical BMI (two dummy variables for overweight and obese) (baseline).




**ESM Fig. 1.** A schematic diagram of analytic samples. SWAN, Study of Women's Health Across the Nation. MPS, Multi-Pollutant Study.




**ESM Fig. 2**. Weights for the PFAS mixtures in association with incidence of diabetes in quantile 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 body mass index (baseline level).