**Associations between Per- and Polyfluoroalkyl Substances and Incident Natural Menopause**

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**Table S1** Baseline participant characteristics overall and by K-means clusters.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristic** | **Total**  **(n=1120)** | **Low**  **(n=143)** | **Low-medium**  **(n=414)** | **Medium-high**  **(n=406)** | **High**  **(n=157)** | **P valuea** |
| Median (IQR)  or n (%) | Median (IQR)  or n (%) | Median (IQR)  or n (%) | Median (IQR)  or n (%) | Median (IQR)  or n (%) |
| Age, years | 48.9 (47.0-50.8) | 49.1 (47.0-50.7) | 49.2 (47.2-51.1) | 48.6 (46.9-50.4) | 48.4 (46.9-50.8) | 0.04 |
| Race/ethnicity |  |  |  |  |  | <.0001 |
| White | 577 (51.5%) | 60 (42.0%) | 199 (48.1%) | 226 (55.7%) | 92 (58.6%) |  |
| Black | 235 (21.0%) | 30 (21.0%) | 63 (15.2%) | 88 (21.7%) | 54 (34.4%) |  |
| Chinese | 142 (12.7%) | 36 (25.1%) | 73 (17.6%) | 33 (8.1%) | 0 (0.0%) |  |
| Japanese | 166 (14.8%) | 17 (11.9%) | 79 (19.1%) | 59 (14.5%) | 11 (7.0%) |  |
| Study site |  |  |  |  |  | <.0001 |
| Southeast MI | 202 (18.0%) | 17 (11.9%) | 67 (16.2%) | 70 (17.2%) | 48 (30.6%) |  |
| Boston, MA | 182 (16.3%) | 23 (16.1%) | 62 (14.9%) | 78 (19.2%) | 19 (12.1%) |  |
| Oakland, CA | 242 (21.6%) | 51 (35.7%) | 115 (27.8%) | 61 (15.0%) | 15 (9.6%) |  |
| Los Angeles, CA | 299 (26.7%) | 34 (23.8%) | 115 (27.8%) | 122 (30.1%) | 28 (17.8%) |  |
| Pittsburgh, PA | 195 (23.4%) | 18 (12.6%) | 55 (13.3%) | 75 (18.5%) | 47 (29.9%) |  |
| Educational attainment |  |  |  |  |  | 0.002 |
| ≤High school | 197 (17.7%) | 28 (19.6%) | 73 (17.7%) | 61 (15.1%) | 35 (22.4%) |  |
| Some college | 350 (31.4%) | 43 (30.0%) | 110 (26.8%) | 144 (35.6%) | 53 (34.0%) |  |
| College | 271 (24.3%) | 48 (33.6%) | 109 (26.5%) | 86 (21.3%) | 28 (18.0%) |  |
| Post-college | 296 (26.6%) | 24 (16.8%) | 119 (29.0%) | 113 (28.0%) | 40 (25.6%) |  |
| Parity |  |  |  |  |  | 0.02 |
| Nulliparous | 215 (19.2%) | 16 (11.2%) | 76 (18.4%) | 92 (22.7%) | 31 (19.8%) |  |
| Parous | 905 (80.8%) | 127 (88.8%) | 338 (81.6%) | 314 (77.3%) | 126 (80.2%) |  |
| Prior hormone use | 248 (22.1%) | 33 (23.1%) | 87 (21.0%) | 83 (20.4%) | 45 (28.7%) |  |
| Smoking status |  |  |  |  |  | 0.001 |
| Never smoker | 720 (64.4%) | 99 (69.7%) | 291 (70.3%) | 246 (60.7%) | 84 (53.5%) |  |
| Former smoker | 291 (26.0%) | 34 (23.9%) | 96 (23.2%) | 109 (26.9%) | 52 (33.1%) |  |
| Current smoker | 107 (9.6%) | 9 (6.3%) | 27 (6.5%) | 50 (12.4%) | 21 (13.4%) |  |
| Physical activity score | 7.9 (6.6-9.0) | 7.5 (6.3-8.8) | 7.9 (6.5-9.1) | 7.9 (6.8-9.0) | 7.7 (6.6-8.6) | 0.11 |
| Body mass index, kg/m2 | 26.1 (22.7-31.5) | 24.6 (22.4-30.2) | 25.6 (22.3-30.1) | 26.4 (22.7-31.8) | 29.4 (24.9-35.1) | <.0001 |

a The significance level was set at 0.05.

**Table S2** Covariates included in the imputation model for FMP age.

|  |
| --- |
| **Covariates related to timing of menopause** |
| Race/ethnicity |
| Study site |
| Frequency of vasomotor symptoms |
| Bleeding pattern |
| Estradiol |
| Follicle-stimulating hormone |
| Day of menstrual cycle corresponding to blood draw |
| Age |
| History of oral contraceptive use |
| History of exogenous hormone use other than oral contraceptives |
| Number of live births |
| Diabetes |
| Cardiovascular disease diagnosis |
| Smoking status |
| Alcohol consumption |
| Body mass index |
| Total physical activity without work |
| Education |
| Financial strain |
| Self-reported health |
| Marital status |
| Employment status |
| Months of amenorrhea reported |

**Table S3** Median (inter-quartile range, IQR) serum concentrations of n-PFOS, Sm-PFOS, PFHxS, PFDoA, PFUnDA, PFDA, PFNA, n-PFOA, and Sb-PFOA by racial/ethnic groups at the MPS baseline (1999-2000).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PFAS serum concentrations, ng/mL** | **Total**  **(n=1120)** | | **Caucasian**  **(n=577)** | | **African American**  **(n=235)** | | **Chinese**  **(n=142)** | | **Japanese**  **(n=166)** | | **P valuea** |
| **%>LOD** | **Median (IQR)** | **%>LOD** | **Median (IQR)** | **%>LOD** | **Median (IQR)** | **%>LOD** | **Median (IQR)** | **%>LOD** | **Median (IQR)** |
| n-PFOS | 100% | 17.1  (12.2-24.5) | 100% | 16.5  (12.0-23.5) | 100% | 21.7  (15.3-32.2) | 100% | 15.6  (10.7-20.1) | 100% | 15.6  (11.2-20.8) | <.0001 |
| Sm-PFOS | 99.9% | 7.2  (4.6-10.8) | 100% | 7.6  (5.2-11.6) | 100% | 8.1  (5.2-12.5) | 99.3% | 4.4  (3.0-6.1) | 100% | 6.9  (4.1-9.3) | <.0001 |
| PFHxS | 99.6% | 1.5  (0.9-2.3) | 99.8% | 1.6  (1.1-2.8) | 99.6% | 1.6  (1.0-2.6) | 99.3% | 1.0  (0.6-1.5) | 99.4% | 1.2  (0.8-1.6) | <.0001 |
| PFUnDA | 30.0% | <LOD  (<LOD-0.2) | 17.9% | <LOD | 33.6% | <LOD  (<LOD-0.2) | 50.7% | 0.15  (<LOD-0.4) | 49.4% | <LOD  (<LOD-0.5) | NA |
| PFDoA | 4.0% | <LOD | 2.6% | <LOD | 8.5% | <LOD | 0.7% | <LOD | 5.4% | <LOD | NA |
| PFDA | 39.3% | <LOD  (<LOD-0.3) | 29.8% | <LOD  (<LOD-0.2) | 47.2% | <LOD  (<LOD-0.3) | 52.1% | 0.15  (<LOD-0.3) | 50.0% | <LOD  (<LOD-0.3) | NA |
| PFNA | 97.0% | 0.6  (0.4-0.8) | 97.4% | 0.5  (0.4-0.7) | 94.5% | 0.6  (0.5-0.8) | 96.5% | 0.6  (0.4-0.8) | 99.4% | 0.6  (0.5-0.8) | <.0001 |
| n-PFOA | 99.9% | 4.0  (2.8-5.7) | 100% | 4.5  (3.3-6.1) | 99.6% | 4.0  (2.8-5.6) | 100% | 2.2  (1.6-3.0) | 100% | 4.0  (3.0-5.2) | <.0001 |
| Sb-PFOA | 18.2% | <LOD | 21.3% | <LOD | 17.4% | <LOD | 12.7% | <LOD | 13.3% | <LOD | NA |

NA, not available. LOD, limit of detection. LOD was 0.1 ng/mL

a Kruskal-Wallis tests were used to examine racial/ethnic differences in median concentrations of PFAS homologues with detection rate >70%. The significance level was set at 0.05.

**Table S4** Hazard ratio (HR) (95% CI) of n-PFOS, Sm-PFOS, n-PFOA, PFNA, and PFHxS serum concentrations on incidence of natural menopause **with surgical menopause excluded instead of censored (n=1051)**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PFAS** | **Tertile of PFAS concentrations** | | | **P value**  **for trendc** | **Per doubling increase**  **HR (95%CI)** | **P valuec** |
| **Tertile 1**  **HR (95%CI)** | **Tertile 2**  **HR (95%CI)** | **Tertile 3**  **HR (95%CI)** |
| **n-PFOS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 10.4 (8.1-12.2) | 16.9 (15.6-18.7) | 28.3 (24.2-37.8) |  |  |  |
| no. cases/person-years | 183/1741 | 192/1719 | 203/1832 |  |  |  |
| Model 1a | Ref | 1.08 (0.88-1.32) | 1.15 (0.93-1.41) | 0.19 | 1.05 (0.95-1.16) | 0.34 |
| Model 2b | Ref | 1.15 (0.93-1.42) | 1.22 (0.98-1.51) | 0.07 | 1.10 (0.99-1.22) | 0.07 |
| **Sm-PFOS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 3.8 (2.9-4.6) | 7.2 (6.2-8.1) | 13.1 (10.9-17.2) |  |  |  |
| no. cases/person-years | 195/1704 | 194/1782 | 189/1807 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.03 (0.84-1.26) | 1.05 (0.85-1.31) | 0.63 | 1.03 (0.94-1.12) | 0.52 |
| Model 2 (Adjusted)b | Ref | 1.11 (0.90-1.37) | 1.18 (0.95-1.48) | 0.14 | 1.07 (0.97-1.17) | 0.16 |
| **n-PFOA** |  |  |  |  |  |  |
| Median (Range), ng/mL | 2.3 (1.8-2.8) | 4.0 (3.5-4.5) | 6.6 (5.6-8.6) |  |  |  |
| no. cases/person-years | 183/1686 | 195/1804 | 200/1802 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.14 (0.92-1.41) | 1.24 (0.99-1.55) | 0.06 | 1.04 (0.93-1.16) | 0.50 |
| Model 2 (Adjusted)b | Ref | 1.12 (0.90-1.39) | 1.26 (1.01-1.58) | 0.04 | 1.08 (0.97-1.21) | 0.16 |
| **PFNA** |  |  |  |  |  |  |
| Median (Range), ng/mL | 0.3 (0.3-0.4) | 0.5 (0.5-0.6) | 0.9 (0.7-1.0) |  |  |  |
| no. cases/person-years | 168/1778 | 181/1572 | 229/1942 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.14 (0.92-1.41) | 1.16 (0.94-1.42) | 0.18 | 1.10 (0.99-1.22) | 0.06 |
| Model 2 (Adjusted)b | Ref | 1.14 (0.91-1.42) | 1.14 (0.92-1.41) | 0.25 | 1.09 (0.98-1.21) | 0.11 |
| **PFHxS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 0.8 (0.6-1.0) | 1.5 (1.3-1.6) | 3.0 (2.3-4.5) |  |  |  |
| no. cases/person-years | 203/1820 | 168/1610 | 207/1862 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 0.92 (0.74-1.13) | 1.10 (0.90-1.35) | 0.36 | 1.03 (0.95-1.11) | 0.48 |
| Model 2 (Adjusted)b | Ref | 1.06 (0.85-1.31) | 1.06 (0.86-1.31) | 0.59 | 1.01 (0.94-1.10) | 0.74 |

**a** Model 1 was adjusted for age at baseline, race/ethnicity, and study site.

b Model 2 was additionally adjusted for education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline.

c The significance level was set at 0.05.

**Table S5** Hazard ratio (HR) (95% CI) of n-PFOS, Sm-PFOS, n-PFOA, PFNA, and PFHxS serum concentrations on incidence of natural menopause **after excluding women who reached natural menopause in 6 months since baseline (n=1091)**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PFAS** | **Tertile of PFAS concentrations** | | | **P value**  **for trendc** | **Per doubling increase**  **HR (95%CI)** | **P valuec** |
| **Tertile 1**  **HR (95%CI)** | **Tertile 2**  **HR (95%CI)** | **Tertile 3**  **HR (95%CI)** |
| **n-PFOS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 10.4 (8.1-12.2) | 16.9 (15.6-18.7) | 28.3 (24.2-37.8) |  |  |  |
| no. cases/person-years | 170/1857 | 185/1880 | 194/1878 |  |  |  |
| Model 1a | Ref | 1.08 (0.88-1.33) | 1.23 (0.99-1.52) | 0.06 | 107 (0.96-1.18) | 0.24 |
| Model 2b | Ref | 1.10 (0.89-1.37) | 1.30 (1.04-1.62) | 0.02 | 1.11 (0.99-1.24) | 0.06 |
| **Sm-PFOS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 3.8 (2.9-4.6) | 7.2 (6.2-8.1) | 13.1 (10.9-17.2) |  |  |  |
| no. cases/person-years | 183/1839 | 185/1920 | 181/1856 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.05 (0.85-1.29) | 1.14 (0.91-1.42) | 0.26 | 1.04 (0.95-1.14) | 0.35 |
| Model 2 (Adjusted)b | Ref | 1.11 (0.89-1.38) | 1.28 (1.02-1.61) | 0.03 | 1.08 (0.99-1.19) | 0.10 |
| **n-PFOA** |  |  |  |  |  |  |
| Median (Range), ng/mL | 2.3 (1.8-2.8) | 4.0 (3.5-4.5) | 6.6 (5.6-8.6) |  |  |  |
| no. cases/person-years | 173/1815 | 184/1933 | 192/1868 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.13 (0.90-1.41) | 1.29 (1.03-1.62) | 0.03 | 1.06 (0.95-1.19) | 0.30 |
| Model 2 (Adjusted)b | Ref | 1.11 (0.88-1.39) | 1.31 (1.04-1.66) | 0.02 | 1.10 (0.98-1.24) | 0.10 |
| **PFNA** |  |  |  |  |  |  |
| Median (Range), ng/mL | 0.3 (0.3-0.4) | 0.5 (0.5-0.6) | 0.9 (0.7-1.0) |  |  |  |
| no. cases/person-years | 163/1928 | 167/1675 | 219/2012 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 1.13 (0.90-1.40) | 1.20 (0.97-1.48) | 0.09 | 1.12 (1.01-1.24) | 0.03 |
| Model 2 (Adjusted)b | Ref | 1.13 (0.90-1.41) | 1.18 (0.95-1.47) | 0.14 | 1.10 (0.99-1.23) | 0.08 |
| **PFHxS** |  |  |  |  |  |  |
| Median (Range), ng/mL | 0.8 (0.6-1.0) | 1.5 (1.3-1.6) | 3.0 (2.3-4.5) |  |  |  |
| no. cases/person-years | 193/1954 | 158/1725 | 198/1936 |  |  |  |
| Model 1 (Unadjusted)a | Ref | 0.90 (0.73-1.12) | 1.15 (0.93-1.41) | 0.21 | 1.05 (0.97-1.13) | 0.25 |
| Model 2 (Adjusted)b | Ref | 1.02 (0.82-1.27) | 1.09 (0.88-1.35) | 0.44 | 1.02 (0.94-1.11) | 0.56 |

**a** Model 1 was adjusted for age at baseline, race/ethnicity, and study site.

b Model 2 was additionally adjusted for education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline.

c The significance level was set at 0.05.

**Table S6** Hazard ratios (HR) (95% confidence intervals, 95% CI) for incident natural menopause with tertile changes and per doubling increase in serum concentrations of n-PFOS, Sm-PFOS, n-PFOA, PFNA, and PFHxS in 720 women who had never smoked before.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PFAS** | **Tertile of PFAS concentrations** | | | ***p* value**  **for trendc** | **Per doubling increase**  **HR (95%CI)** | ***p* valuec** |
| **Tertile 1**  **HR (95%CI)** | **Tertile 2**  **HR (95%CI)** | **Tertile 3**  **HR (95%CI)** |
| **n-PFOS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 10.4 (8.1-12.2) | 16.9 (15.6-18.7) | 28.3 (24.2-37.8) |  |  |  |
| no. cases/person-years | 116/1243 | 134/1311 | 116/1109 |  |  |  |
| Model 1a | Ref | 1.10 (0.86-1.41) | 1.27 (0.97-1.66) | 0.08 | 1.09 (0.95-1.25) | 0.20 |
| Model 2b | Ref | 1.03 (0.80-1.33) | 1.26 (0.95-1.66) | 0.12 | 1.12 (0.97-1.29) | 0.13 |
| **Sm-PFOS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 3.8 (2.9-4.5) | 7.1 (6.2-8.0) | 13.0 (10.7-16.8) |  |  |  |
| no. cases/person-years | 135/1301 | 121/1259 | 110/1104 |  |  |  |
| Model 1a | Ref | 1.07 (0.83-1.38) | 1.19 (0.90-1.57) | 0.23 | 1.07 (0.95-1.19) | 0.27 |
| Model 2b | Ref | 1.06 (0.82-1.38) | 1.26 (0.95-1.69) | 0.12 | 1.08 (0.96-1.22) | 0.19 |
| **n-PFOA** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 2.3 (1.8-2.8) | 4.0 (3.5-4.5) | 6.6 (5.6-8.6) |  |  |  |
| no. cases/person-years | 133/1331 | 126/1299 | 107/1035 |  |  |  |
| Model 1a | Ref | 1.17 (0.89-1.53) | 1.32 (0.98-1.77) | 0.06 | 1.09 (0.94-1.25) | 0.27 |
| Model 2b | Ref | 1.14 (0.86-1.50) | 1.35 (1.00-1.83) | 0.05 | 1.10 (0.94-1.27) | 0.23 |
| **PFNA** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 0.3 (0.3-0.4) | 0.5 (0.5-0.6) | 0.9 (0.7-1.0) |  |  |  |
| no. cases/person-years | 103/1360 | 125/1087 | 138/1217 |  |  |  |
| Model 1a | Ref | 1.49 (1.14-1.95) | 1.44 (1.10-1.87) | 0.008 | 1.23 (1.08-1.39) | 0.002 |
| Model 2b | Ref | 1.52 (1.16-2.00) | 1.39 (1.05-1.83) | 0.03 | 1.19 (1.04-1.36) | 0.01 |
| **PFHxS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 0.8 (0.6-1.0) | 1.5 (1.3-1.6) | 3.0 (2.3-4.5) |  |  |  |
| no. cases/person-years | 146/1439 | 98/1139 | 122/1086 |  |  |  |
| Model 1a | Ref | 0.85 (0.66-1.11) | 1.30 (1.01-1.68) | 0.07 | 1.08 (0.98-1.19) | 0.13 |
| Model 2b | Ref | 0.97 (0.74-1.27) | 1.21 (0.93-1.57) | 0.17 | 1.06 (0.96-1.18) | 0.23 |

**a** Model 1 was adjusted for age at baseline, race/ethnicity, and study site.

b Model 2 was additionally adjusted for education, parity, BMI at baseline, physical activity, and prior hormone use at baseline.

**Table S7 Pooled** HR (95% CI) for incident natural menopause with tertile changes and per doubling increase in serum concentrations of n-PFOS, Sm-PFOS, n-PFOA, PFNA, and PFHxS in 720 women who had never smoked before **with 10 imputations**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **PFAS** | **Tertile of PFAS concentrations** | | | **P value**  **for trendc** | **Per doubling increase**  **HR (95%CI)** | **P valuec** |
| **Tertile 1**  **HR (95%CI)** | **Tertile 2**  **HR (95%CI)** | **Tertile 3**  **HR (95%CI)** |
| **n-PFOS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 10.4 (8.1-12.2) | 16.9 (15.6-18.7) | 28.3 (24.2-37.8) |  |  |  |
| no. cases/person-yearsa | 216/1204 | 228/1221 | 216/1030 |  |  |  |
| Model 1b | Ref | 1.00 (0.82-1.22) | 1.32 (1.06-1.65) | 0.01 | 1.13 (1.01-1.27) | 0.02 |
| Model 2c | Ref | 0.98 (0.80-1.21) | 1.33 (1.06-1.67) | 0.02 | 1.13 (1.01-1.28) | 0.03 |
| **Sm-PFOS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 3.8 (2.9-4.6) | 7.2 (6.2-8.1) | 13.1 (10.9-17.2) |  |  |  |
| no. cases/person-yearsa | 234/1268 | 221/1143 | 205/1044 |  |  |  |
| Model 1b | Ref | 1.05 (0.85-1.29) | 1.23 (0.97-1.55) | 0.09 | 1.10 (1.00-1.21) | 0.05 |
| Model 2c | Ref | 1.05 (0.85-1.31) | 1.27 (1.00-1.63) | 0.05 | 1.11 (1.01-1.23) | 0.04 |
| **n-PFOA** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 2.3 (1.8-2.8) | 4.0 (3.5-4.5) | 6.6 (5.6-8.6) |  |  |  |
| no. cases/person-yearsa | 238/1264 | 225/1225 | 197/966 |  |  |  |
| Model 1b | Ref | 1.05 (0.85-1.29) | 1.26 (1.01-1.59) | 0.05 | 1.12 (1.00-1.25) | 0.04 |
| Model 2c | Ref | 1.05 (0.85-1.30) | 1.29 (1.01-1.63) | 0.03 | 1.13 (1.01-1.27) | 0.03 |
| **PFNA** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 0.3 (0.3-0.4) | 0.5 (0.5-0.6) | 0.9 (0.7-1.0) |  |  |  |
| no. cases/person-yearsa | 212/1287 | 207/1036 | 241/1133 |  |  |  |
| Model 1b | Ref | 1.16 (0.94-1.45) | 1.28 (1.03-1.60) | 0.02 | 1.11 (1.00-1.23) | 0.05 |
| Model 2c | Ref | 1.19 (0.95-1.50) | 1.27 (1.01-1.59) | 0.04 | 1.10 (0.99-1.22) | 0.08 |
| **PFHxS** |  |  |  |  |  |  |
| Median (IQR), ng/mL | 0.8 (0.6-1.0) | 1.5 (1.3-1.6) | 3.0 (2.3-4.5) |  |  |  |
| no. cases/person-yearsa | 252/1367 | 199/1028 | 209/1060 |  |  |  |
| Model 1b | Ref | 1.14 (0.93-1.42) | 1.20 (0.98-1.48) | 0.07 | 1.08 (0.99-1.17) | 0.06 |
| Model 2c | Ref | 1.02 (0.86-1.23) | 1.09 (0.88-1.36) | 0.10 | 1.07 (0.99-1.17) | 0.10 |

a Averaged no. cases and person-years from 10 imputations. b Model 1 was adjusted for age at baseline, race/ethnicity, and study site.

b Model 2 was additionally adjusted for education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline.

**Table S8** Adjusted HR (95% CI) of incident natural menopause with per doubling increase in serum concentrations of n-PFOS, Sm-PFOS, n-PFOA, PFNA, and PFHxS in 720 women who had never smoked before.

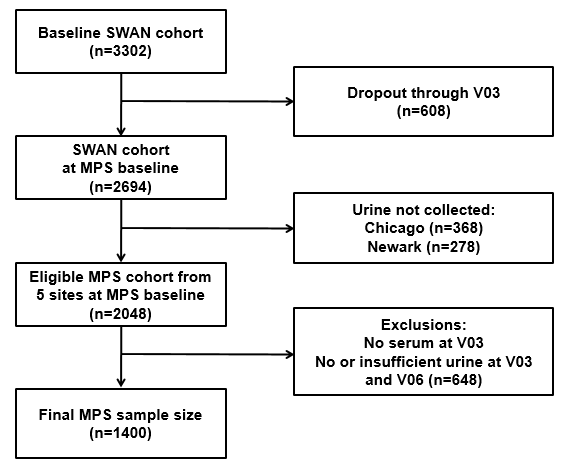
|  |  |  |  |
| --- | --- | --- | --- |
| **PFAS** | **Racial/ethnic groups** | | |
| **White**  **(n=343)** | **Black**  **(n=134)** | **Asian**  **(n=243)** |
| no. cases/person-years |  |  |  |
|  | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **n-PFOS** | 1.26 (1.03-1.55) | 1.16 (0.88-1.52) | 0.94 (0.74-1.19) |
| **Sm-PFOS** | 1.18 (1.00-1.41) | 1.13 (0.89-1.43) | 0.95 (0.80-1.14) |
| **n-PFOA** | 1.29 (1.04-1.59) | 1.06 (0.79-1.42) | 0.89 (0.71-1.11) |
| **PFNA** | 1.54 (1.24-1.91) | 1.15 (0.84-1.58) | 0.94 (0.78-1.14) |
| **PFHxS** | 1.30 (1.12-1.52) | 1.12 (0.93-1.35) | 0.85 (0.73-1.01) |

**Table S9** Hazard ratio (HR) (95% CI) of natural menopause incidence with by PFAS clusters.

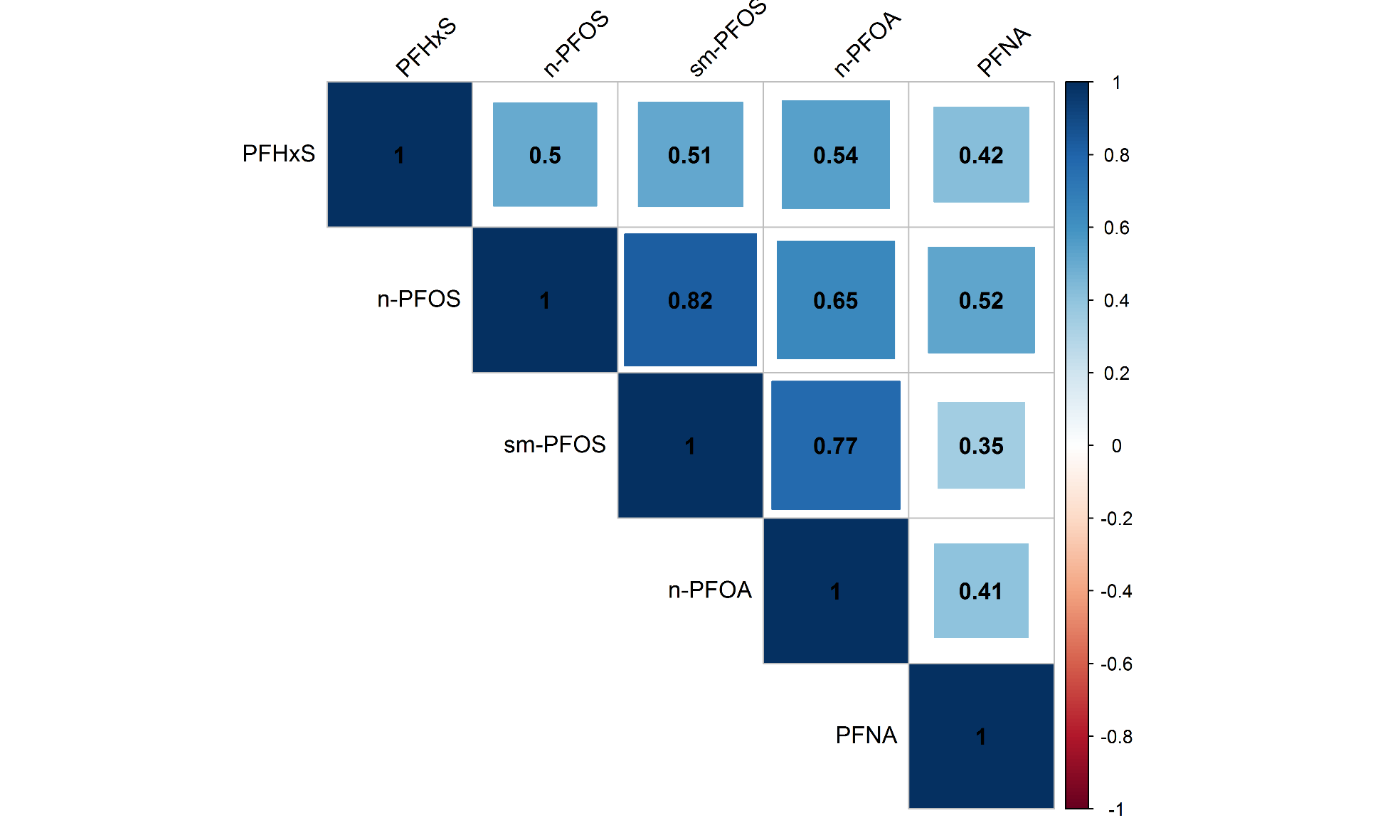
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PFAS cluster** | **Population clusters** | | | |
| **Cluster 1**  **HR (95%CI)** | **Cluster 2**  **HR (95%CI)** | **Cluster 3**  **HR (95%CI)** | **Cluster 4**  **HR (95%CI)** |
| no. cases/person-years | 68/765 | 220/2010 | 209/2122 | 81/727 |
| Model 1a | Ref | 1.31  (0.98-1.75) | 1.33  (0.96-1.85) | 1.60  (1.07-2.39) |
| Model 2b | Ref | 1.30  (0.97-1.68) | 1.31  (0.94-1.83) | 1.63  (1.08-2.45) |

**a** Model 1 was adjusted for age at baseline, race/ethnicity, and study site.

b Model 2 was additionally adjusted for education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline.

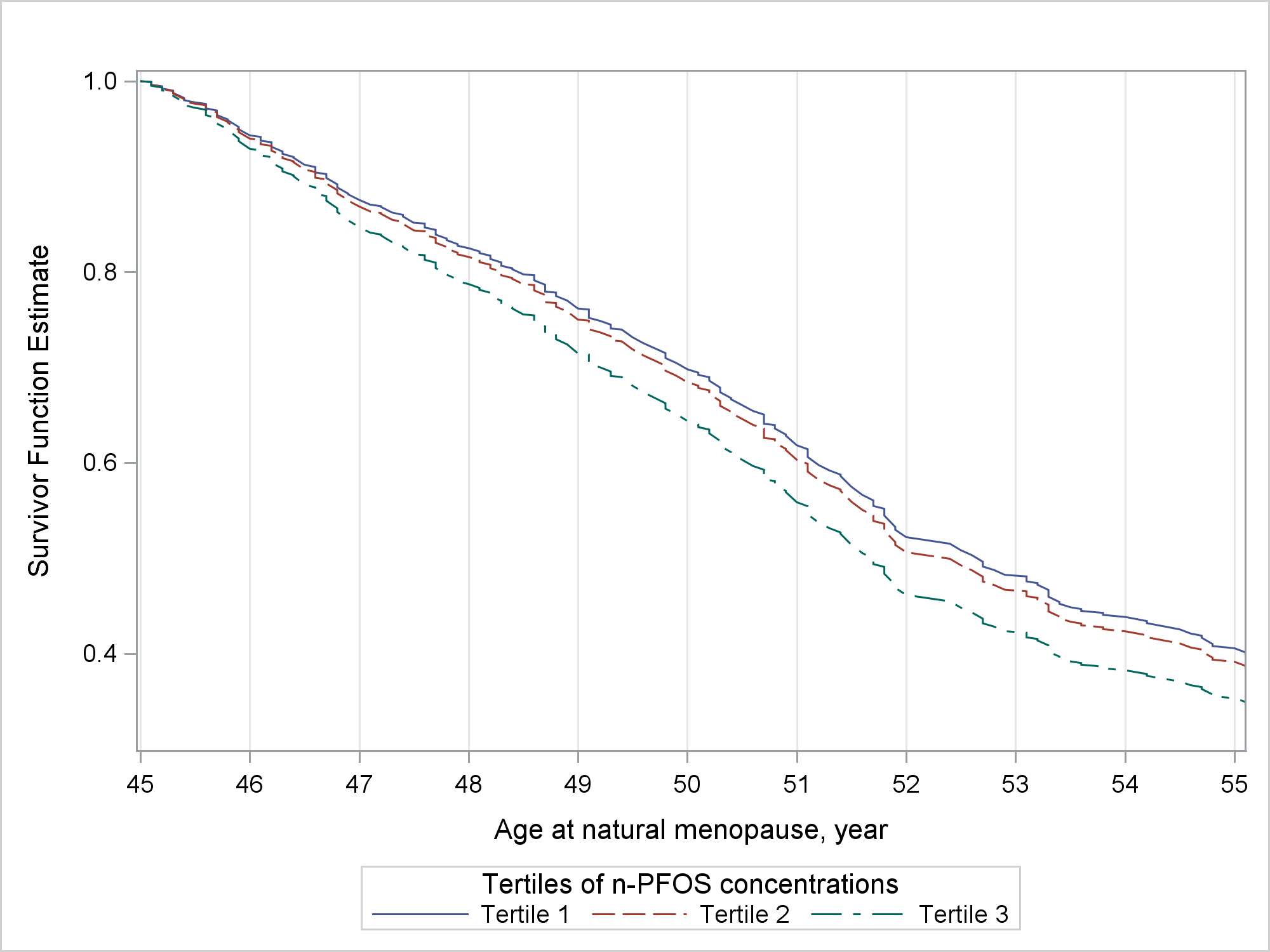


**Figure S1** The study designs of the Study of Women’s Health Across the Nation (SWAN) Multi-Pollutant Study (MPS).

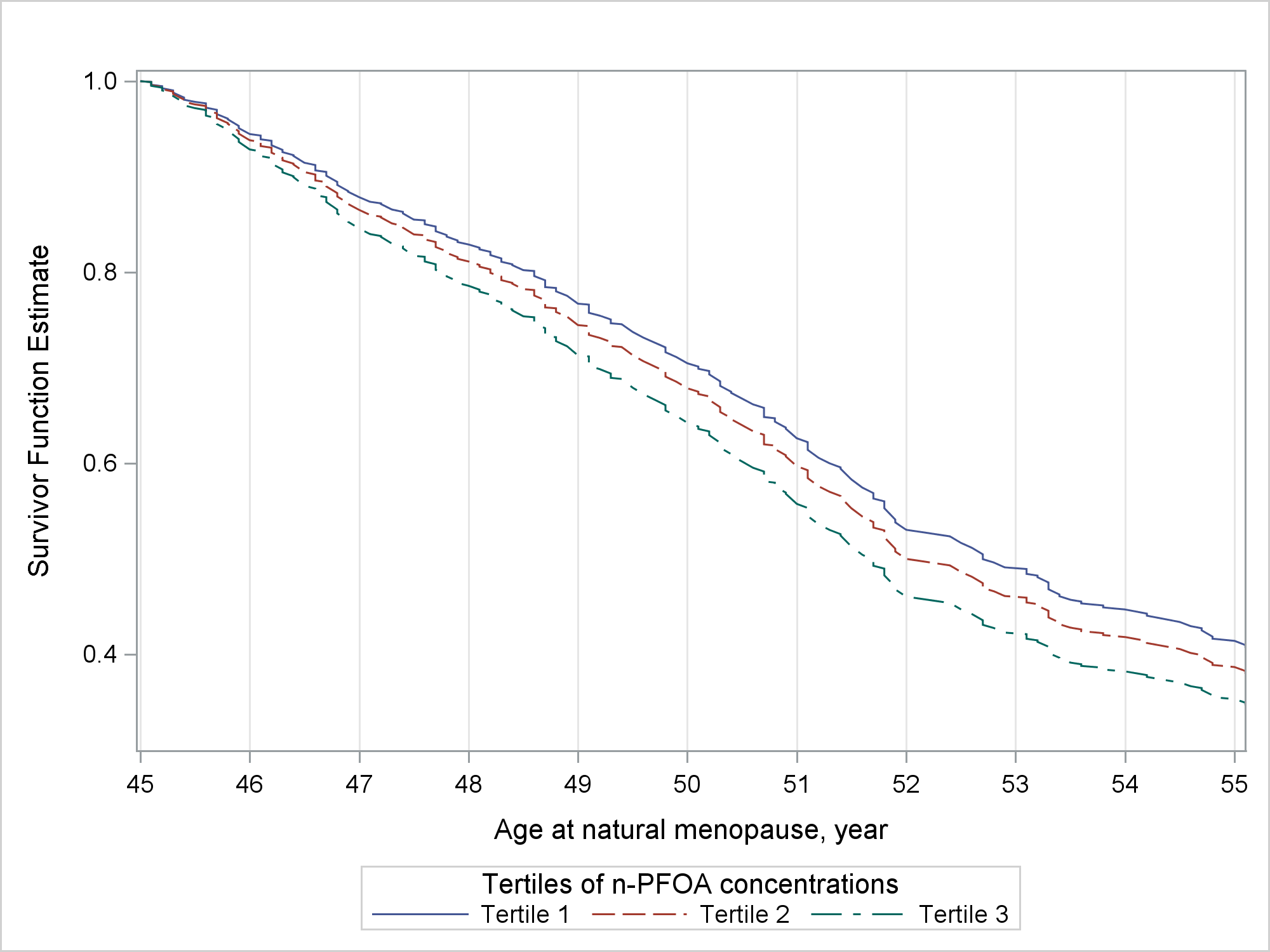
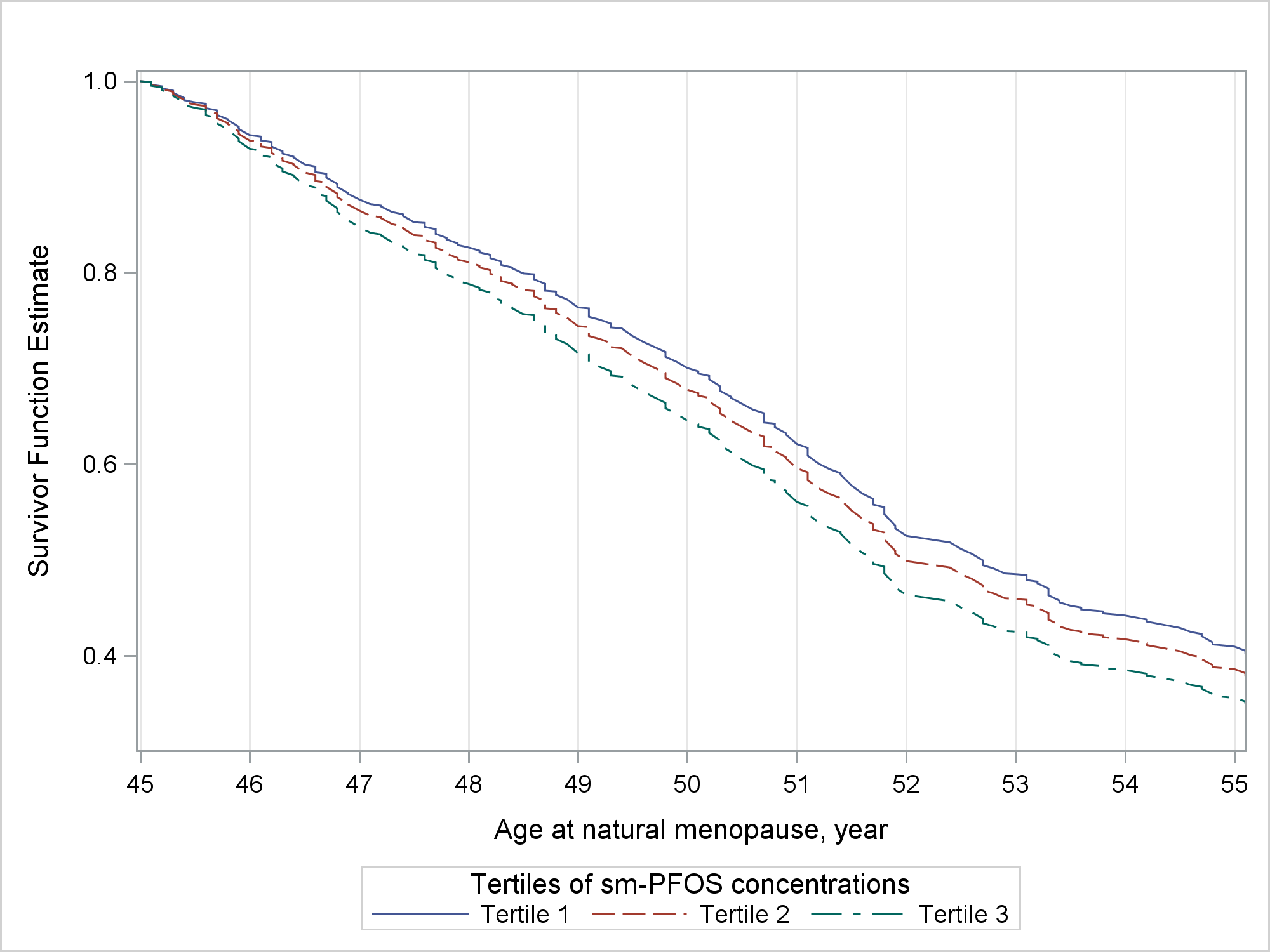


**Figure S2** Spearman correlation matrix of PFAS biomarkers in SWAN 1999-2000.

**Figure S3** Adjusted survival curves of natural menopause by tertiles of n-PFOS serum concentrations. The model was adjusted for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. The hazards ratio of tertile 2 and tertile 3 was 1.06 (0.86-1.31) and 1.26 (1.02-1.57), compared to tertile 1 (*ptrend*=0.03). The predicted median age at natural menopause was for tertile 1 was 52.6 years, and 52.3 years, and 51.6 years for tertiles 2 and 3, respectively.

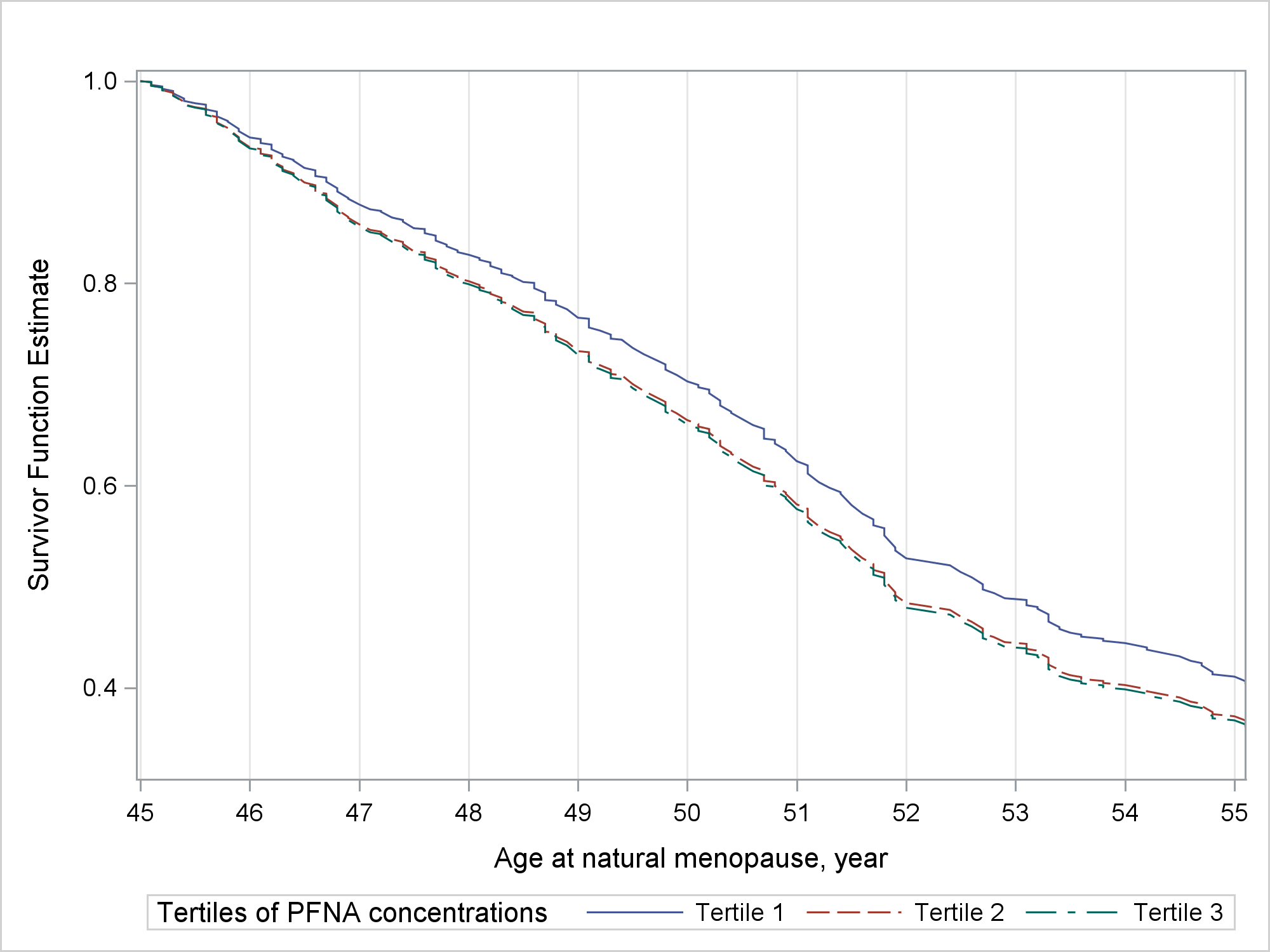


**Figure S4** Adjusted survival curves of natural menopause by tertiles of Sm-PFOS serum concentrations. The model was adjusted for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. The hazards ratio of tertile 2 and tertile 3 was 1.11 (0.90-1.37) and 1.27 (1.01-1.59), compared to tertile 1 (*ptrend*=0.03). The predicted median age at natural menopause for tertile 1 was 52.6 years, and 51.9 years, and 51.7 years for tertiles 2 and 3, respectively.

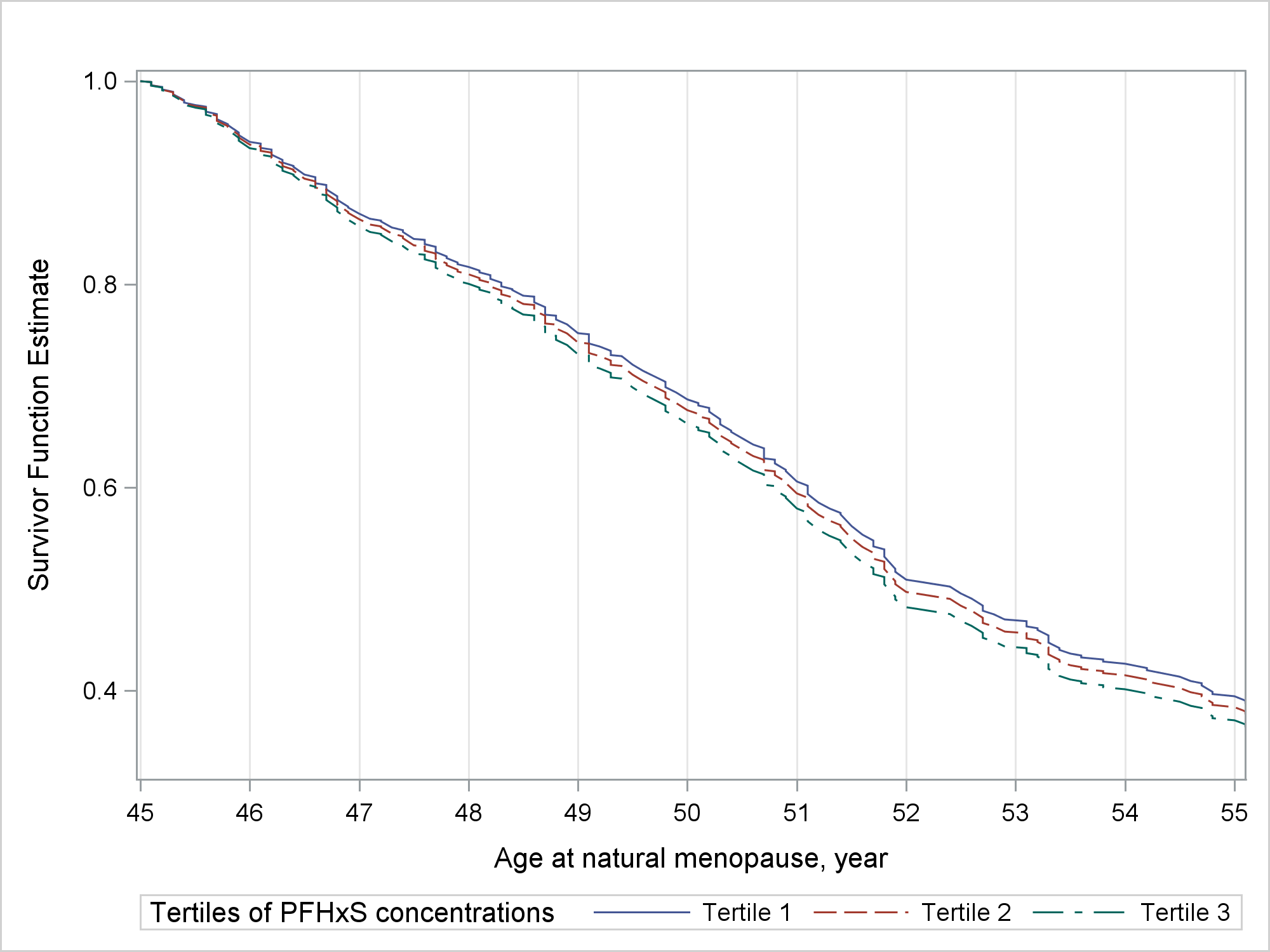


**Figure S5** Adjusted survival curves of natural menopause by tertiles of n-PFOA serum concentrations. The model was adjusted for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. The hazards ratio of tertile 2 and tertile 3 was 1.12 (0.90-1.40) and 1.31 (1.04-1.65), compared to tertile 1 (*ptrend*=0.01). The predicted median age at natural menopause for tertile 1 was 52.7 years, and 51.9 years, and 51.6 years for tertiles 2 and 3, respectively.

**Figure S6** Adjusted survival curves of natural menopause by tertiles of PFNA serum concentrations. The model was adjusted for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. The hazards ratio of tertile 2 and tertile 3 was 1.18 (0.95-1.47) and 1.20 (0.97-1.49), compared to tertile 1 (*ptrend*=0.10). The predicted median age at natural menopause for tertile 1 was 52.7 years, and 51.8 years, and 51.8 years for tertiles 2 and 3, respectively.



**Figure S7** Adjusted survival curves of natural menopause by tertiles of PFHxS serum concentrations. The model was adjusted for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. The hazards ratio of tertile 2 and tertile 3 was 1.05 (0.84-1.30) and 1.11 (0.90-1.37), compared to tertile 1 (*ptrend*=0.33). The predicted median age at natural menopause for tertile 1 was 52.4 years, and 51.9 years, and 51.8 years for tertiles 2 and 3, respectively.



1. Exposure to **n-PFOS** and incidence of natural menopause by racial groups



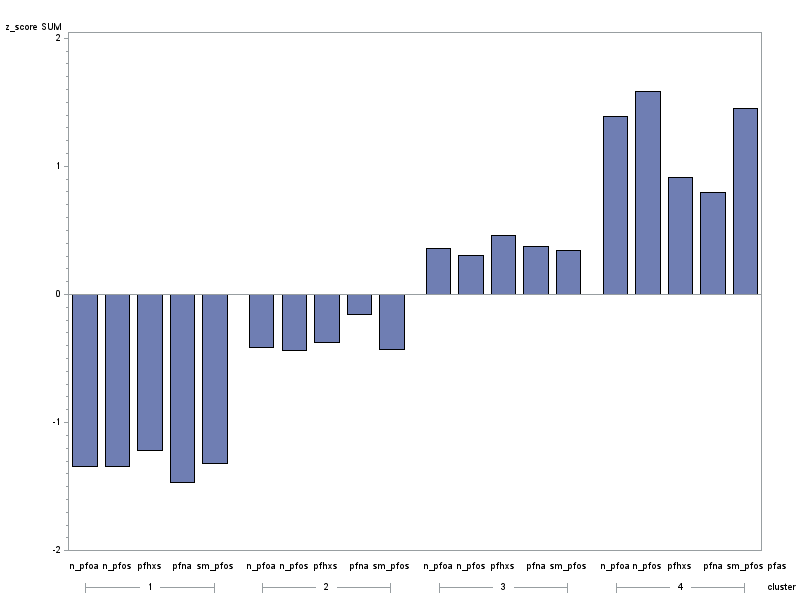
1. Exposure to **Sm-PFOS** and incidence of natural menopause by racial groups



1. Exposure to **PFHxS** and incidence of natural menopause by racial groups



**Figure S8** Adjusted hazard ratio (HR) (95% confidence interval, 95% CI) of natural menopause incidence with per doubling increase in serum concentrations of n-PFOS, Sm-PFOS and PFHxS. Models were adjusted for age at baseline, study site, education, parity, BMI at baseline, physical activity, smoking status, and prior hormone use at baseline. *P* values for the interaction terms with race/ethnicity are 0.54 for n-PFOS, 0.52 for Sm-PFOS, and 0.03 for PFHxS.



**Figure S9** Cluster means of the 5 standardized log-transformed serum PFAS concentrations using k-means clustering. Y-axis (cluster means) represents the mean standardized z-scores of log2-transformed PFAS concentrations. Cluster 1 (n=143): “low” overall PFAS concentration pattern; clusters 2 (n=414): “moderate low” overall PFAS concentration pattern; cluster 3 (n=406): “moderate high” overall PFAS concentration pattern; cluster 4 (n=157): “high” overall PFAS concentration pattern.