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Supplemental Material

Per- and Polyfluoroalkyl Substances (PFAS) and Lipid Trajectories in Women 45–56 Years of Age: The Study of Women's Health Across the Nation

Habyeong Kang, Ning Ding, Carrie A. Karvonen-Gutierrez, Bhramar Mukherjee, Antonia M. Calafat, and Sung Kyun Park

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Figure S3. Odds ratios (●) and their 95% confidence intervals (bar) for associations of tertiles of PFAS concentrations (versus tertile 1) or PFAS mixture (versus low concentration) with trajectories (high versus low trajectories) of (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, and (D) triglycerides when the models were not adjusted for BMI in the SWAN-MPS cohort (1999–2016, n = 1130). The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, physical activity, and total energy intake. The numbers at the right side of the bars represent odds ratios and their 95% confidence intervals. Results with continuous PFAS concentrations can be found in supplemental Table S14.

Figure S4. Means of the standardized log-transformed serum PFAS concentrations in each cluster identified by k-means clustering in the SWAN-MPS cohort (1999–2016, n = 1130). Cluster 1 (n=291): "low" overall PFAS concentration pattern; clusters 2 (n=569): "medium" overall PFAS concentration pattern; cluster 3 (n=270): "high" overall PFAS concentration pattern.

References

Table S1. Detection frequencies and concentrations of serum PFAS in the SWAN-MPS cohort (1999–2016, n = 1130).

	Detected frequency		Concentration (ng/mL)				
	n	%	Geometric mean	1st quartile	Median	3rd quartile	Maximum
n- PFOA	1129	99.9	4.1	2.8	4.1	5.8	56.5
PFNA	1096	97.0	0.5	0.4	0.6	0.8	4.4
PFDA	456	40.4	-	<0.1	<0.1	0.2	2.6
PFUnDA	352	31.2	-	<0.1	<0.1	0.2	3.8
PFDoDA	39	3.5	-	<0.1	<0.1	<0.1	2.6
n-PFOS	1129	99.9	17.7	12.5	17.4	24.4	250
Sm-PFOS	1128	99.8	7.2	4.7	7.3	11.0	126.0
PFHxS	1125	99.6	1.6	1.0	1.5	2.4	46.5
MeFOSAA	1127	99.7	1.5	0.9	1.5	2.3	11.5
EtFOSAA	1120	99.1	1.3	0.7	1.2	2.2	112.5

Table S2. Timeline of measurements of variables used in this study.

	SWAN baseline	SWAN-MPS baseline (Visit 3)	Visit 4	Visit 5	Visit 6	Visit 7	Visit 9	Visit 12	Visit 13	Visit 15
	1996-1997	1999-2001	2000-2002	2001-2003	2002-2004	2003-2005	2005-2007	2009-2011	2011-2013	2015-2016
Serum PFAS		O								
Blood lipids		O	O	O	O	O	O	O	O	O
Lipid-lowering medication		O	O	O	O	O	O	O	O	O
Study site	O									
Race/ethnicity	O									
Education	O									
Age		O								
Menopausal status		O								
Smoking status		O								
Alcohol consumption		O								
Body mass index		O								
Physical activity		O								
Total energy intake	O									

Table S3. Constant values added to measured lipid concentrations (mg/dL) for those with the statin or non-statin medication depending on race/ethnicity (Wu et al. 2007).

	Statin medication			Non-statin medication		
	White	Black	Chinese or Japanese	White	Black	Chinese or Japanese
Total cholesterol	+50.7	+50.7	+50.7	+46.1	+20.1	+20.1
LDL cholesterol	+48.1	+48.1	+48.1	+40.1	+11.4	+11.4
HDL cholesterol	-2.3	-0.4	-2.0	-5.9	-3.1	-3.1
Triglycerides	+19.7	+19.7	+19.7	+59.0	+59.0	+59.0

Table S4. Criteria to select a best model for total cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130, adding constant methods).

	Number of Class = 2			Number of Class = 3			Number of Class = 4		
	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability
Polynomial									
Linear	39%	99460	0.971	19%	97728	0.946	8%	96868	0.475
+quadratic	39%	99379	0.971	19%	97625	0.946	8%	96762	0.291
+cubic	39%	99370	0.971	19%	97609	0.947	8%	96752	0.478
Natural cubic spline									
2 knots (tertile)	39%	99374	0.971	19%	97614	0.947	8%	96756	0.377
2 knots (equidistance)	39%	99363	0.971	19%	**97602**	0.947	8%	96744	0.452
3 knots (quartile)	39%	99377	0.971	19%	97621	0.947	8%	96769	0.452
3 knots (equidistance)	39%	99371	0.971	19%	97615	0.947	8%	96757	0.672
4 knots (quintile)	39%	99393	0.971	19%	97645	0.947	8%	96799	0.596
4 knots (equidistance)	39%	99388	0.971	19%	97640	0.947	8%	96789	0.597

Natural cubic spline model with 2 knots (equidistance) and three classes was selected.

Table S5. Criteria to select a best model for LDL cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130, adding constant methods).

	Number of Class = 2			Number of Class = 3			Number of Class = 4		
	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability
Polynomial									
Linear	36%	92729	0.970	20%	90698	0.955	7%	89882	0.328
+quadratic	36%	92643	0.971	20%	90587	0.956	7%	89759	0.651
+cubic	36%	90587	0.971	20%	90542	0.957	8%	89711	0.648
Natural cubic spline									
2 knots (tertile)	36%	92612	0.971	20%	**90522**	0.957	8%	89679	0.455
2 knots (equidistance)	36%	92631	0.971	20%	90560	0.957	7%	89732	0.646
3 knots (quartile)	36%	92630	0.971	20%	90551	0.957	7%	89707	0.329
3 knots (equidistance)	36%	92634	0.971	20%	90554	0.957	7%	89715	0.646
4 knots (quintile)	36%	92645	0.971	20%	90569	0.958	7%	89726	0.329
4 knots (equidistance)	36%	92621	0.971	20%	90540	0.957	8%	89697	0.649

Natural cubic spline model with 2 knots (tertile) and three classes was selected.

Table S6. Criteria to select a best model for HDL cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130, adding constant methods).

	Number of Class = 2			Number of Class = 3			Number of Class = 4		
	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability
Polynomial									
Linear	41%	79595	0.976	20%	77128	0.962	13%	76120	0.588
+quadratic	41%	79613	0.976	20%	77151	0.963	13%	76153	0.587
+cubic	41%	79614	0.976	20%	77157	0.963	13%	76161	0.450
Natural cubic spline									
2 knots (tertile)	41%	79590	0.976	20%	77122	0.963	13%	76118	0.486
2 knots (equidistance)	41%	79626	0.976	20%	77172	0.963	13%	76181	0.450
3 knots (quartile)	41%	79595	0.976	20%	77128	0.963	13%	76132	0.376
3 knots (equidistance)	41%	79619	0.976	20%	77158	0.963	13%	76173	0.374
4 knots (quintile)	41%	79592	0.976	20%	77121	0.964	13%	76132	0.587
4 knots (equidistance)	41%	79544	0.976	20%	**77063**	0.963	13%	76050	0.488

Natural cubic spline model with 4 knots (equidistance) and three classes was selected.

Table S7. Criteria to select a best model for triglycerides trajectories in the SWAN-MPS cohort (1999–2016, n = 1130, adding constant methods).

	Number of Class = 2			Number of Class = 3			Number of Class = 4		
	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability	Smallest membership %	BIC	Average posterior probability
Polynomial									
Linear	38%	**8784**	0.977	10%	6999	0.962	8%	6039	0.378
+quadratic	38%	8787	0.977	10%	7001	0.962	8%	6049	0.346
+cubic	38%	8790	0.977	10%	7012	0.962	8%	6064	0.347
Natural cubic spline									
2 knots (tertile)	38%	8792	0.977	10%	7013	0.962	8%	6065	0.613
2 knots (equidistance)	38%	8792	0.977	10%	7014	0.962	8%	6067	0.424
3 knots (quartile)	38%	8809	0.977	10%	7039	0.962	8%	6099	0.509
3 knots (equidistance)	38%	8809	0.977	10%	7040	0.962	8%	6101	0.425
4 knots (quintile)	38%	8827	0.977	10%	7066	0.962	8%	6135	0.426
4 knots (equidistance)	38%	8826	0.977	10%	7065	0.962	8%	6133	0.348

Linear model with two classes was selected.

Table S8. Classification of study participants in the SWAN-MPS cohort (1999–2016, n = 1130) by lipids trajectories from two different methods (Adding constant and covariate methods).

		Adding constant method										
		Total cholesterol			LDL cholesterol			HDL cholesterol			Triglycerides	
		Low	Middle	High	Low	Middle	High	Low	Middle	High	Low	High
Covariate method	Low	341	15	0	342	6	0	417	16	0	707	30
	Middle	20	535	8	26	530	20	10	446	7	-	-
	High	0	7	204	0	10	196	0	6	228	9	384
Misclassification		4.4%			5.5%			3.5%			3.5%	

Table S9. Associations of serum concentrations of total PFOS, PFDA, PFUnDA, MeFOSAA, and EtFOSAA with trajectories of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Total cholesterol			LDL cholesterol			HDL cholesterol			Triglycerides		
	Trajectory	OR (95% CI)[a]	p-value[b]	Trajectory	OR (95% CI)	p-value	Trajectory	OR (95% CI)	p-value	Trajectory	OR (95% CI)	p-value
Total PFOS (per doubling)	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.09 (0.92, 1.28)	0.57	Middle (n=546)	1.16 (0.99, 1.36)	0.15	Middle (n=468)	1.02 (0.87, 1.20)	0.96	High (n=414)	0.88 (0.75, 1.02)	0.16
	High (n=212)	1.21 (0.99, 1.49)	0.11	High (n=216)	1.28 (1.04, 1.56)	0.04	High (n=235)	0.97 (0.79, 1.20)	0.95			
PFDA (deteted vs. non-detected)	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.37 (1.04, 1.8)	0.12	Middle (n=546)	1.24 (0.94, 1.63)	0.17	Middle (n=468)	1.14 (0.87, 1.51)	0.85	High (n=414)	0.70 (0.53, 0.92)	0.10
	High (n=212)	1.56 (1.11, 2.19)	0.05	High (n=216)	1.53 (1.10, 2.14)	0.04	High (n=235)	1.39 (0.99, 1.96)	0.45			
PFUnDA (deteted vs. non-detected)	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=717)	1.00	
	Middle (n=557)	1.36 (1.02, 1.82)	0.12	Middle (n=546)	1.31 (0.98, 1.74)	0.15	Middle (n=468)	1.44 (1.07, 1.92)	0.15	High (n=415)	0.79 (0.58, 1.07)	0.18
	High (n=212)	1.58 (1.13, 2.22)	0.05	High (n=216)	1.60 (1.15, 2.23)	0.04	High (n=235)	1.29 (0.92, 1.81)	0.45			
MeFOSAA (per doubling)	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=718)	1.00	
	Middle (n=557)	1.04 (0.90, 1.19)	0.78	Middle (n=546)	1.16 (1.01, 1.34)	0.15	Middle (n=468)	1.00 (0.87, 1.16)	0.96	High (n=416)	0.98 (0.85, 1.12)	0.75
	High (n=212)	1.15 (0.96, 1.37)	0.15	High (n=216)	1.15 (0.96, 1.37)	0.17	High (n=235)	1.02 (0.86, 1.22)	0.95			
EtFOSAA (per doubling)	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=719)	1.00	
	Middle (n=557)	0.98 (0.88, 1.09)	0.78	Middle (n=546)	1.05 (0.94, 1.16)	0.43	Middle (n=468)	1.01 (0.89, 1.11)	0.96	High (n=417)	0.89 (0.80, 0.99)	0.12
	High (n=212)	0.93 (0.81, 1.06)	0.30	High (n=216)	1.00 (0.88, 1.14)	0.99	High (n=235)	0.94 (0.82, 1.08)	0.76			

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) comparing detected vs. non-detected PFDA or PFUnDA, or per doubling of MeFOSAA or EtFOSAA concentration.
[b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake.

Table S10. Associations of tertiles of serum PFAS concentrations with total cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Trajectory class	PFAS tertile 2 vs. 1		PFAS tertile 3 vs. 1	
		OR (95% CI)[a]	p-value[b]	OR (95% CI)	p-value
n-PFOA	Low (n=361)	1.00		1.00	
	Middle (n=557)	0.90 (0.67, 1.17)	0.67	0.89 (0.68, 1.17)	0.53
	High (n=212)	0.73 (0.56, 0.95)	0.03	0.90 (0.70, 1.15)	0.40
PFNA	Low (n=361)	1.00		1.00	
	Middle (n=557)	1.22 (0.93, 1.60)	0.30	1.06 (0.81, 1.39)	0.77
	High (n=212)	2.21 (1.73, 2.83)	<0.0001	1.18 (0.90, 1.55)	0.27
Total PFOS	Low (n=361)	1.00		1.00	
	Middle (n=557)	1.56 (1.19, 2.03)	0.009	1.25 (0.95, 1.64)	0.32
	High (n=212)	1.71 (1.35, 2.18)	<0.0001	1.70 (1.33, 2.17)	0.0002
n-PFOS	Low (n=361)	1.00		1.00	
	Middle (n=557)	1.44 (1.10, 1.87)	0.13	1.22 (0.93, 1.60)	0.32
	High (n=212)	1.61 (1.27, 2.04)	0.0002	1.61 (1.27, 2.06)	<0.0001
Sm-PFOS	Low (n=361)	1.00		1.00	
	Middle (n=557)	1.33 (1.02, 1.73)	0.11	1.25 (0.95, 1.65)	0.32
	High (n=212)	1.31 (1.02, 1.68)	0.04	1.65 (1.29, 2.11)	0.002
PFHxS	Low (n=361)	1.00		1.00	
	Middle (n=557)	0.96 (0.73, 1.26)	0.77	1.21 (0.92, 1.59)	0.32
	High (n=212)	1.66 (1.30, 2.12)	0.0001	1.63 (1.29, 2.05)	0.002
MeFOSAA	Low (n=361)	1.00		1.00	
	Middle (n=557)	0.93 (0.71, 1.21)	0.74	0.99 (0.76, 1.29)	0.96
	High (n=212)	1.34 (1.05, 1.72)	0.03	1.50 (1.18, 1.91)	0.001
EtFOSAA	Low (n=361)	1.00		1.00	
	Middle (n=557)	0.96 (0.74, 1.25)	0.77	0.89 (0.69, 1.16)	0.53
	High (n=212)	1.02 (0.80, 1.32)	0.86	0.76 (0.59, 0.97)	0.04
PFAS	Low (n=361)	1.00		1.00	
mixture	Middle (n=557)	1.24 (0.95, 1.62)	0.26	1.25 (0.93, 1.69)	0.32
	High (n=212)	1.38 (1.06, 1.80)	0.03	1.69 (1.36, 2.12)	0.0003

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) for association of tertiles of PFAS concentrations (versus tertile 1) with total cholesterol trajectories (versus low trajectory). [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake. Cut off points for PFAS tertile groups: 3.4 and 5.3 ng/mL for total PFOA, 0.6 and 0.8 ng/mL for PFNA, 14.2 and 21.4 ng/mL for n-PFOS, 5.7 and 9.4 ng/mL for Sm-PFOS, and 1.2 and 2.0 ng/mL for PFHxS.

Table S11. Associations of tertiles of serum PFAS concentrations with LDL cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Trajectory class	PFAS tertile 2 vs. 1		PFAS tertile 3 vs. 1	
		OR (95% CI)[a]	p-value[b]	OR (95% CI)	p-value
n-PFOA	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.07 (0.82, 1.40)	0.69	1.20 (0.91, 1.57)	0.33
	High (n=216)	0.89 (0.68, 1.15)	0.37	1.05 (0.83, 1.35)	0.67
PFNA	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.22 (0.93, 1.60)	0.33	1.14 (0.87, 1.49)	0.45
	High (n=216)	1.96 (1.53, 2.51)	<0.0001	1.09 (0.84, 1.43)	0.58
Total PFOS	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.42 (1.08, 1.86)	0.10	1.40 (1.06, 1.84)	0.12
	High (n=216)	1.97 (1.56, 2.49)	<0.0001	1.94 (1.54, 2.45)	<0.0001
n-PFOS	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.25 (0.96, 1.64)	0.30	1.31 (1.00, 1.73)	0.08
	High (n=216)	1.85 (1.47, 2.34)	<0.0001	1.89 (1.50, 2.38)	<0.0001
Sm-PFOS	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.16 (0.89, 1.53)	0.49	1.48 (1.12, 1.96)	0.05
	High (n=216)	1.56 (1.22, 2.00)	0.0007	1.92 (1.52, 2.42)	<0.0001
PFHxS	Low (n=368)	1.00		1.00	
	Middle (n=546)	0.98 (0.74, 1.28)	0.85	1.19 (0.90, 1.56)	0.33
	High (n=216)	1.37 (1.07, 1.74)	0.02	1.41 (1.12, 1.78)	0.006
MeFOSAA	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.12 (0.86, 1.46)	0.51	1.31 (1.01, 1.70)	0.12
	High (n=216)	1.39 (1.09, 1.79)	0.01	1.43 (1.13, 1.81)	0.006
EtFOSAA	Low (n=368)	1.00		1.00	
	Middle (n=546)	1.13 (0.87, 1.46)	0.51	0.98 (0.75, 1.28)	0.89
	High (n=216)	1.30 (1.02, 1.66)	0.04	0.91 (0.72, 1.16)	0.58
PFAS	Low (n=368)	1.00		1.00	
mixture	Middle (n=546)	1.40 (1.06, 1.83)	0.16	1.41 (1.04, 1.92)	0.52
	High (n=216)	1.57 (1.21, 2.03)	0.001	1.79 (1.44, 2.22)	<0.0001

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) for association of tertiles of PFAS concentrations (versus tertile 1) with total cholesterol trajectories (versus low trajectory). [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake.Cut off points for PFAS tertile groups: 3.4 and 5.3 ng/mL for total PFOA, 0.6 and 0.8 ng/mL for PFNA, 14.2 and 21.4 ng/mL for n-PFOS, 5.7 and 9.4 ng/mL for Sm-PFOS, and 1.2 and 2.0 ng/mL for PFHxS.

Table S12. Associations of tertiles of serum PFAS concentrations with HDL cholesterol trajectories in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Trajectory class	PFAS tertile 2 vs. 1		PFAS tertile 3 vs. 1	
		OR (95% CI)[a]	p-value[b]	OR (95% CI)	p-value
n-PFOA	Low (n=427)	1.00		1.00	
	Middle (n=468)	0.95 (0.73, 1.24)	0.79	0.83 (0.63, 1.10)	0.72
	High (n=235)	0.79 (0.61, 1.04)	0.17	0.77 (0.60, 1.01)	0.21
PFNA	Low (n=427)	1.00		1.00	
	Middle (n=468)	0.91 (0.70, 1.19)	0.65	0.94 (0.72, 1.23)	0.97
	High (n=235)	0.86 (0.66, 1.11)	0.36	0.95 (0.72, 1.25)	0.72
Total PFOS	Low (n=427)	1.00		1.00	
	Middle (n=468)	1.16 (0.90, 1.50)	0.38	1.01 (0.77, 1.31)	0.97
	High (n=235)	1.08 (0.84, 1.40)	0.54	0.81 (0.62, 1.05)	0.23
n-PFOS	Low (n=427)	1.00		1.00	
	Middle (n=468)	1.23 (0.95, 1.59)	0.29	0.98 (0.75, 1.27)	0.97
	High (n=235)	1.12 (0.87, 1.44)	0.51	0.83 (0.63, 1.07)	0.23
Sm-PFOS	Low (n=427)	1.00		1.00	
	Middle (n=468)	0.82 (0.63, 1.06)	0.29	0.74 (0.57, 0.96)	0.21
	High (n=235)	0.63 (0.48, 0.82)	0.003	0.57 (0.44, 0.75)	0.0005
PFHxS	Low (n=427)	1.00		1.00	
	Middle (n=468)	1.27 (0.97, 1.65)	0.29	0.98 (0.75, 1.29)	0.97
	High (n=235)	1.10 (0.84, 1.42)	0.54	1.22 (0.94, 1.58)	0.23
MeFOSAA	Low (n=427)	1.00		1.00	
	Middle (n=468)	1.03 (0.79, 1.34)	0.85	0.85 (0.66, 1.11)	0.72
	High (n=235)	1.39 (1.08, 1.80)	0.03	0.94 (0.72, 1.22)	0.71
EtFOSAA	Low (n=427)	1.00		1.00	
	Middle (n=468)	0.85 (0.66, 1.10)	0.38	0.99 (0.77, 1.29)	0.96
	High (n=235)	0.62 (0.48, 0.82)	0.003	0.79 (0.61, 1.02)	0.21
PFAS	Low (n=427)	1.00		1.00	
mixture	Middle (n=468)	1.42 (1.09, 1.86)	0.006	0.87 (0.65, 1.17)	0.82
	High (n=235)	1.26 (0.96, 1.65)	0.16	0.85 (0.66, 1.10)	0.29

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) for association of tertiles of PFAS concentrations (versus tertile 1) with total cholesterol trajectories (versus low trajectory). [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake. Cut off points for PFAS tertile groups: 3.4 and 5.3 ng/mL for total PFOA, 0.6 and 0.8 ng/mL for PFNA, 14.2 and 21.4 ng/mL for n-PFOS, 5.7 and 9.4 ng/mL for Sm-PFOS, and 1.2 and 2.0 ng/mL for PFHxS.

Table S13. Associations of tertiles of serum PFAS concentrations with triglycerides trajectories in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Trajectory class	PFAS tertile 2 vs. 1		PFAS tertile 3 vs. 1	
		OR (95% CI)[a]	p-value[b]	OR (95% CI)	p-value
n-PFOA	Low (n=716)	1.00		1.00	
	High (n=414)	0.93 (0.67, 1.29)	0.88	0.80 (0.56, 1.13)	0.36
PFNA	Low (n=716)	1.00		1.00	
	High (n=414)	1.00 (0.73, 1.38)	0.98	0.78 (0.56, 1.08)	0.29
Total PFOS	Low (n=716)	1.00		1.00	
	High (n=414)	0.87 (0.63, 1.19)	0.84	0.72 (0.52, 1.00)	0.22
n-PFOS	Low (n=716)	1.00		1.00	
	High (n=414)	0.86 (0.63, 1.18)	0.84	0.71 (0.51, 0.99)	0.22
Sm-PFOS	Low (n=716)	1.00		1.00	
	High (n=414)	1.07 (0.77, 1.48)	0.88	0.90 (0.64, 1.26)	0.56
PFHxS	Low (n=716)	1.00		1.00	
	High (n=414)	1.13 (0.82, 1.55)	0.84	0.90 (0.65, 1.26)	0.56
MeFOSAA	Low (n=716)	1.00		1.00	
	High (n=414)	1.03 (0.74, 1.41)	0.98	0.86 (0.62, 1.19)	0.54
EtFOSAA	Low (n=716)	1.00		1.00	
	High (n=414)	1.19 (0.87, 1.63)	0.84	0.73 (0.52, 1.03)	0.22
PFAS	Low (n=716)	1.00		1.00	
Mixture	High (n=414)	0.79 (0.58, 1.09)	0.84	0.86 (0.59, 1.26)	0.56

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) for association of tertiles of PFAS concentrations (versus tertile 1) with total cholesterol trajectories (versus low trajectory). [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake. Cut off points for PFAS tertile groups: 3.4 and 5.3 ng/mL for total PFOA, 0.6 and 0.8 ng/mL for PFNA, 14.2 and 21.4 ng/mL for n-PFOS, 5.7 and 9.4 ng/mL for Sm-PFOS, and 1.2 and 2.0 ng/mL for PFHxS.

Table S14. Associations of serum PFAS concentrations with trajectories of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides when the models were not adjusted for BMI in the SWAN-MPS cohort (1999–2016, n = 1130).

PFAS	Total cholesterol			LDL cholesterol			HDL cholesterol			Triglycerides		
	Trajectory	OR (95% CI)[a]	p-value[b]	Trajectory	OR (95% CI)	p-value	Trajectory	OR (95% CI)	p-value	Trajectory	OR (95% CI)	p-value
n-PFOA	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	0.99 (0.84, 1.17)	0.83	Middle (n=546)	0.99 (0.84, 1.17)	0.83	Middle (n=468)	0.94 (0.80, 1.11)	0.34	High (n=414)	0.94 (0.80, 1.10)	0.71
	High (n=212)	0.95 (0.77, 1.16)	0.43	High (n=216)	0.95 (0.77, 1.16)	0.98	High (n=235)	0.85 (0.69, 1.04)	0.06	-	-	
PFNA	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.07 (0.91, 1.25)	0.41	Middle (n=546)	1.10 (0.94, 1.29)	0.22	Middle (n=468)	1.13 (0.96, 1.33)	0.13	High (n=414)	0.84 (0.73, 0.98)	0.03
	High (n=212)	1.21 (0.98, 1.49)	0.08	High (n=216)	1.18 (0.96, 1.44)	0.11	High (n=235)	1.09 (0.89, 1.34)	0.39	-	-	
Total PFOS	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.08 (0.93, 1.27)	0.31	Middle (n=546)	1.16 (0.99, 1.36)	0.06	Middle (n=468)	0.97 (0.83, 1.14)	0.72	High (n=414)	0.95 (0.82, 1.10)	0.50
	High (n=212)	1.19 (0.98, 1.45)	0.08	High (n=216)	1.28 (1.05, 1.55)	0.01	High (n=235)	0.83 (0.68, 1.02)	0.07	-	-	
n-PFOS	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.08 (0.92, 1.27)	0.33	Middle (n=546)	1.14 (0.97, 1.34)	0.10	Middle (n=468)	1.00 (0.85, 1.17)	0.99	High (n=414)	0.92 (0.80, 1.07)	0.29
	High (n=212)	1.20 (0.98, 1.46)	0.08	High (n=216)	1.28 (1.05, 1.56)	0.01	High (n=235)	0.87 (0.71, 1.07)	0.18	-	-	
Sm-PFOS	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.10 (0.96, 1.25)	0.18	Middle (n=546)	1.19 (1.04, 1.36)	0.01	Middle (n=468)	0.91 (0.79, 1.04)	0.16	High (n=414)	1.05 (0.92, 1.19)	0.48
	High (n=212)	1.17 (0.99, 1.40)	0.07	High (n=216)	1.25 (1.05, 1.49)	0.01	High (n=235)	0.81 (0.68, 0.96)	0.02	-	-	
PFHxS	Low (n=361)	1.00		Low (n=368)	1.00		Low (n=427)	1.00		Low (n=716)	1.00	
	Middle (n=557)	1.16 (1.03, 1.30)	0.02	Middle (n=546)	1.12 (0.99, 1.26)	0.06	Middle (n=468)	1.06 (0.94, 1.20)	0.32	High (n=414)	0.98 (0.88, 1.10)	0.73
	High (n=212)	1.17 (1.00, 1.36)	0.05	High (n=216)	1.11 (0.96, 1.29)	0.16	High (n=235)	1.12 (0.96, 1.30)	0.15	-	-	

[a] Odds ratios (ORs) and their 95% confidence intervals (CIs) per doubling of each PFAS concentration. [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, physical activity, and total energy intake.

Table S15. Cross-sectional association of serum PFAS concentrations (ng/mL) with blood lipid levels at baseline (mg/dL) in the SWAN-MPS cohort (1999–2016, n = 1130).

	Total cholesterol		LDL cholesterol		HDL cholesterol		log(triglycerides)	
	Effect size (95% CI)[a]	p-value[b]	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value
n-PFOA	-1.48 (-4.16, 1.20)	0.38	-0.45 (-2.87, 1.96)	0.71	0.35 (-0.70, 1.40)	0.52	-0.04 (-0.08, -0.01)	0.03
PFNA	0.85 (-1.62, 3.31)	0.50	1.38 (-0.84, 3.60)	0.28	0.43 (-0.54, 1.39)	0.48	-0.04 (-0.07, -0.01)	0.04
n-PFOS	1.37 (-1.20, 3.94)	0.38	1.85 (-0.46, 4.17)	0.28	0.73 (-0.28, 1.74)	0.40	-0.04 (-0.08, -0.01)	0.03
Sm-PFOS	2.36 (0.20, 4.52)	0.16	2.47 (0.53, 4.42)	0.06	0.43 (-0.42, 1.28)	0.48	-0.02 (-0.04, 0.01)	0.21
PFHxS	0.98 (-0.90, 2.85)	0.38	1.11 (-0.58, 2.80)	0.28	0.53 (-0.21, 1.26)	0.40	-0.02 (-0.04, 0.01)	0.17

[a] Increases in lipid levels and their 95% confidence intervals (CIs) per doubling of each PFAS concentration. [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake.

Table S16. Association of serum PFAS concentrations (ng/mL) with rate of change in blood lipid levels during follow-up (mg/dL/year) in the SWAN-MPS cohort (1999–2016, n = 1130).

	Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides	
	Effect size (95% CI)[a]	p-value[b]	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value
Rate of lipid change from baseline to Visit 6 (on average 3.01 years of follow-up, n=1095)								
n-PFOA	0.43 (-0.26, 1.11)	0.55	0.28 (-0.33, 0.90)	0.76	-0.12 (-0.36, 0.12)	0.52	1.35 (0.14, 2.57)	0.15
PFNA	0.14 (-0.49, 0.77)	0.74	0.12 (-0.44, 0.69)	0.76	-0.01 (-0.23, 0.21)	0.92	0.19 (-0.93, 1.32)	0.74
n-PFOS	-0.31 (-0.96, 0.35)	0.60	-0.21 (-0.80, 0.38)	0.76	-0.31 (-0.54, -0.08)	0.04	1.08 (-0.09, 2.26)	0.18
Sm-PFOS	-0.38 (-0.93, 0.17)	0.55	-0.03 (-0.79, 0.19)	0.76	-0.15 (-0.34, 0.04)	0.33	0.34 (-0.64, 1.32)	0.62
PFHxS	0.08 (-0.40, 0.56)	0.74	0.07 (-0.36, 0.50)	0.76	-0.05 (-0.22, 0.12)	0.72	0.31 (-0.54, 1.17)	0.62
Rate of lipid change from baseline to Visit 9 (on average 5.98 years of follow-up, n=1026)								
n-PFOA	0.19 (-0.22, 0.59)	0.95	0.06 (-0.27, 0.38)	0.85	0.00 (-0.14, 0.15)	0.98	0.51 (-0.18, 1.20)	0.34
PFNA	-0.01 (-0.38, 0.35)	0.95	-0.10 (-0.39, 0.19)	0.85	0.03 (-0.10, 0.16)	0.98	0.18 (-0.45, 0.80)	0.72
n-PFOS	0.03 (-0.35, 0.40)	0.95	-0.07 (-0.38, 0.23)	0.85	-0.07 (-0.20, 0.07)	0.98	0.53 (-0.12, 1.17)	0.34
Sm-PFOS	0.04 (-0.28, 0.37)	0.95	-0.03 (-0.30, 0.23)	0.85	-0.05 (-0.17, 0.07)	0.98	0.36 (-0.20, 0.92)	0.34
PFHxS	0.01 (-0.26, 0.29)	0.95	-0.02 (-0.25, 0.20)	0.85	0.01 (-0.09, 0.11)	0.98	0.02 (-0.46, 0.50)	0.93
Rate of lipid change from baseline to Visit 12 (on average 10.69 years of follow-up, n=956)								
n-PFOA	-0.10 (-0.35, 0.14)	0.50	-0.11 (-0.31, 0.08)	0.53	-0.02 (-0.11, 0.07)	0.83	0.32 (-0.90, 0.73)	0.15
PFNA	0.10 (-0.12, 0.32)	0.50	0.00 (-0.17, 0.17)	0.93	0.02 (-0.06, 0.10)	0.83	0.41 (0.05, 0.78)	0.06
n-PFOS	-0.03 (-0.27, 0.20)	0.79	-0.09 (-0.28, 0.09)	0.53	-0.04 (-0.13, 0.05)	0.83	0.51 (0.13, 0.90)	0.05
Sm-PFOS	-0.10 (-0.29, 0.10)	0.50	-0.11 (-0.26, 0.05)	0.53	-0.04 (-0.12, 0.03)	0.83	0.26 (-0.06, 0.59)	0.15
PFHxS	0.09 (-0.08, 0.26)	0.50	0.03 (-0.11, 0.16)	0.83	0.01 (-0.06, 0.07)	0.83	0.21 (-0.08, 0.49)	0.15

[a] Increases in rate of change in lipid levels and their 95% confidence intervals (CIs) per doubling of each PFAS concentration. [b] Adjusted p-value based on false discovery rate. The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, BMI, physical activity, and total energy intake.

Method for literature review of studies on the association of PFAS exposure with lipids

We conducted a search of research articles in PubMed database up until June 2022 using relevant keywords. We limited the studies that measured blood concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and/or triglycerides as outcomes. Given a plenty of cross-sectional studies published on this topic, we only included those that involved a sample size greater than 500 or those that included a population with high exposure (e.g., occupational exposure). All available longitudinal studies were included regardless of their sample sizes.

Table S17 Summary of results of selected epidemiological studies[a] on associations between PFAS and lipids.

Reference, study population, and note	Lipid	Result
Cross-sectional study, general population		
Château-Degat et al. 2010 Canadian Inuit (n=723)	Total cholesterol	PFOS: positive association
	LDL cholesterol	PFOS: null association
	HDL cholesterol	PFOS: positive association
	Triglycerides	PFOS: null association
Eriksen et al. 2013 Danish midlife adults (n=753)	Total cholesterol	PFOA: positive association PFOS: positive association
Fisher et al. 2013 Canadian adults (n=3496)	Total cholesterol	PFOA: null association PFOS: null association PFHxS: positive association
	LDL cholesterol	PFOA: null association PFOS: null association PFHxS: positive association
	HDL cholesterol	PFOA: null association PFOS: null association PFHxS: null association
	Triglycerides	PFOA: null association PFOS: null association PFHxS: null association
Liu et al. 2018 US adults (NHANES, n=1871)	Total cholesterol	PFOA: positive association PFOS: null association
	LDL cholesterol	PFOA: null association PFOS: null association
	HDL cholesterol	PFOA: positive association PFOS: positive association
	Triglycerides	PFOA: inverse association PFOS: inverse association
Cong et al. 2021 Chinese older adults (n=1238)	Total cholesterol	PFOA: positive association PFOS: positive association
	LDL cholesterol	PFOA: positive association PFOS: positive association
	HDL cholesterol	PFOA: null association PFOS: null association
	Triglycerides	PFOA: null association PFOS: null association

Table S17 (Continued)

Reference, study population, and note	Lipid	Result
Cross-sectional study, population with high exposure		
Steenland et al. 2009 US adults with high exposure to PFOA via contaminated drinking water (n=46294)	Total cholesterol	PFOA: positive association PFOS: positive association
	LDL cholesterol	PFOA: positive association PFOS: positive association
	HDL cholesterol	PFOA: null association PFOS: null association
	Triglycerides	PFOA: positive association PFOS: positive association
Wang et al. 2012 Chinese residents living near fluorochemical plants (n=132)	Total cholesterol	PFOA: null association
	LDL cholesterol	PFOA: null association
	HDL cholesterol	PFOA: null association
	Triglycerides	PFOA: null association
Canova et al. 2020 Italian young adults with high exposure to PFAS via contaminated drinking water (n=15720)	Total cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	LDL cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	HDL cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	Triglycerides	PFOA: positive association PFOS: null association PFHxS: positive association
Li et al. 2020 Swedish adults with recent exposure to PFAS via contaminated drinking water (n=1160)	Total cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	LDL cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	HDL cholesterol	PFOA: positive association PFOS: positive association PFHxS: positive association
	Triglycerides	PFOA: null association PFOS: inverse association PFHxS: null association

Table S17 (Continued)

Reference, study population, and note	Lipid	Result
Cross-sectional study, occupational population		
Wang et al. 2012 Workers exposed to PFAS (n=55)	Total cholesterol	PFOA: null association
	LDL cholesterol	PFOA: null association
	HDL cholesterol	PFOA: inverse association
	Triglycerides	PFOA: null association
Longitudinal study, general population		
Donat-Vargas et al. 2019 Swedish adults (n=187) ** PFAS and lipids were measured at baseline and follow-up (10-year interval). The average PFAS concentrations were associated with lipids at follow-up.*	Total cholesterol	PFOA: null association PFNA: null association PFOS: null association PFHxS: null association
	Triglycerides	PFOA: null association PFNA: inverse association PFOS: inverse association PFHxS: null association
Lin et al. 2019 US adults with overweight or prediabetic symptoms (n=888) ** A randomized controlled trial was conducted with two groups (lifestyle intervention and placebo), and the participants were followed-up for ~15 years.*	Hypercholesterolemia	PFOA: null association PFNA: positive association only in placebo group PFOS: null association PFHxS: null association
	Hypertriglyceridemia	PFOA: positive association PFNA: positive association PFOS: positive association only in placebo group PFHxS: positive association

Table S17 (Continued)

Reference, study population, and note	Lipid	Result
Dunder et al. 2022 Swedish older adults (n=864) ** Changes in PFAS concentrations over 10 years were associated with changes in lipids over 10 years.*	Total cholesterol	PFOA: positive association PFNA: positive association PFOS: null association PFHxS: positive association
	LDL cholesterol	PFOA: null association PFNA: null association PFOS: null association PFHxS: null association
	HDL cholesterol	PFOA: positive association PFNA: positive association PFOS: positive association PFHxS: positive association
	Triglycerides	PFOA: positive association PFNA: positive association PFOS: null association PFHxS: positive association
Longitudinal study, population with high exposure		
Fitz-Simon et al. 2013 US adults with high exposure to PFOA via contaminated drinking water (n=560) ** Changes in PFAS concentrations over 4 years were associated with changes in lipids levels.*	Total cholesterol	PFOA: positive association PFOS: positive association
	LDL cholesterol	PFOA: positive association PFOS: positive association
	HDL cholesterol	PFOA: null association PFOS: null association
	Triglycerides	PFOA: null association PFOS: null association
Winquist and Steenland 2015 US adults with high exposure to PFOA via contaminated drinking water (n=28541)	Hypercholesterolemia	PFOA: positive association
Longitudinal study, occupational population		
Olsen et al. 2003 Workers exposed to PFAS (n=174) ** Mixed effect models with repeated measures were used.*	Total cholesterol	PFOA: positive association PFOS: null association
	Triglycerides	PFOA: positive association PFOS: null association

Table S17 (Continued)

Reference, study population, and note	Lipid	Result
Sakr et al. 2007 Workers exposed to PFOA (n=454) ** Mixed effect models with repeated measures were used.*	Total cholesterol	PFOA: positive association
	LDL cholesterol	PFOA: null association
	HDL cholesterol	PFOA: null association
	Triglycerides	PFOA: null association
[a] Comprehensive review on this issue can be found in previous literature (Andersen et al. 2021; ATSDR 2021; Fragki et al. 2021)		

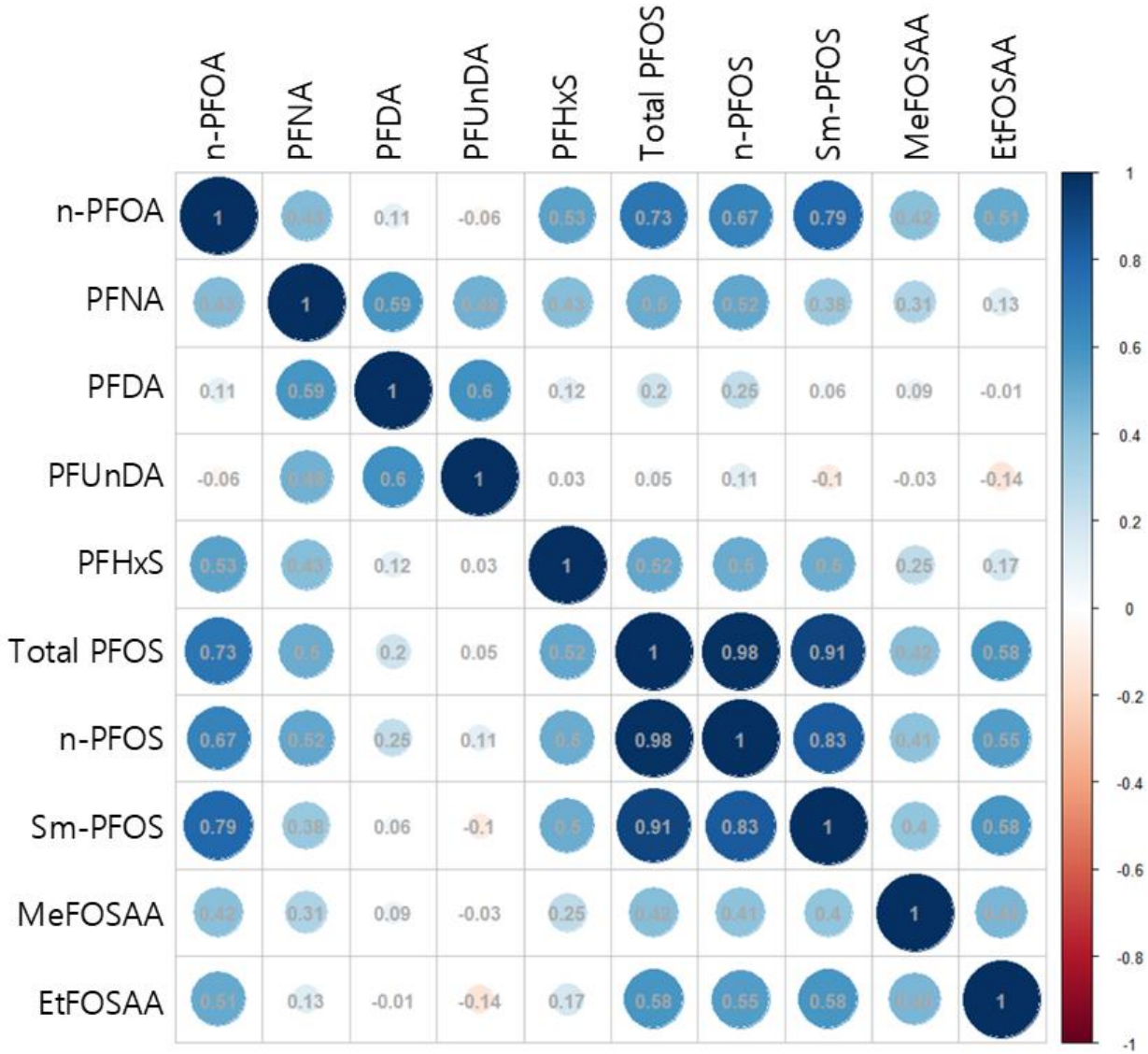

Figure S1. Spearman's correlations between serum PFAS concentrations in the SWAN-MPS cohort (1999–2016, n = 1130).

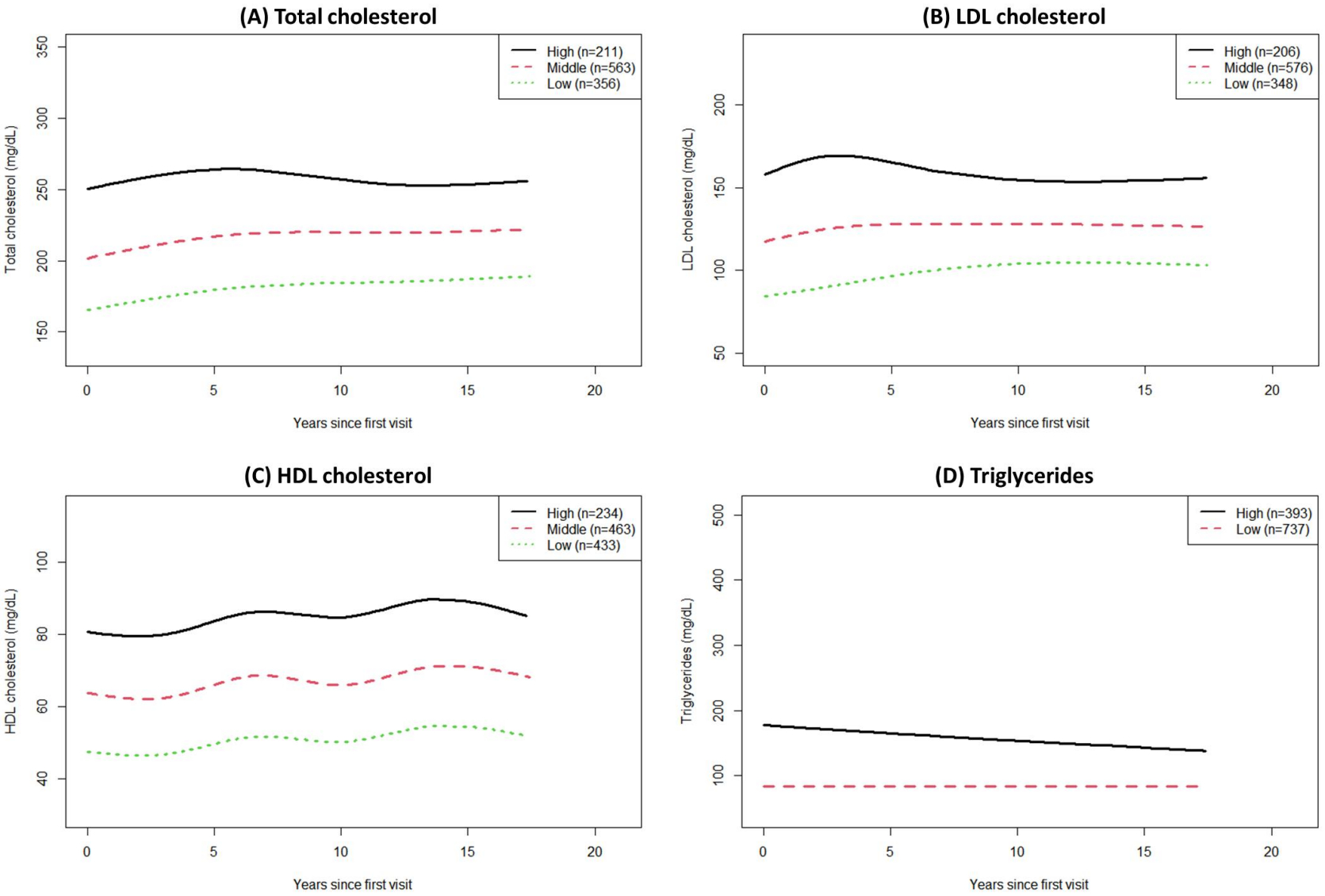
(A) Total cholesterol
High (n=211)
Middle (n=563)
Low (n=356)
Total cholesterol (mg/dL)
150
200
250
300
350
0
5
10
15
20
Years since first visit
(B) LDL cholesterol
High (n=206)
Middle (n=576)
Low (n=348)
LDL cholesterol (mg/dL)
50
100
150
200
0
5
10
15
20
Years since first visit
(C) HDL cholesterol
High (n=234)
Middle (n=463)
Low (n=433)
HDL cholesterol (mg/dL)
40
60
80
100
0
5
10
15
20
Years since first visit
(D) Triglycerides
High (n=393)
Low (n=737)
Triglycerides (mg/dL)
100
200
300
400
500
0
5
10
15
20
Years since first visit

Figure S2. Trajectories of (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, and (D) triglycerides identified by latent class growth model in the SWAN-MPS cohort (1999–2016, n = 1130). 'Covariate method' (described in the Methods of the main text) was applied to consider lipid-lowering medication effects.

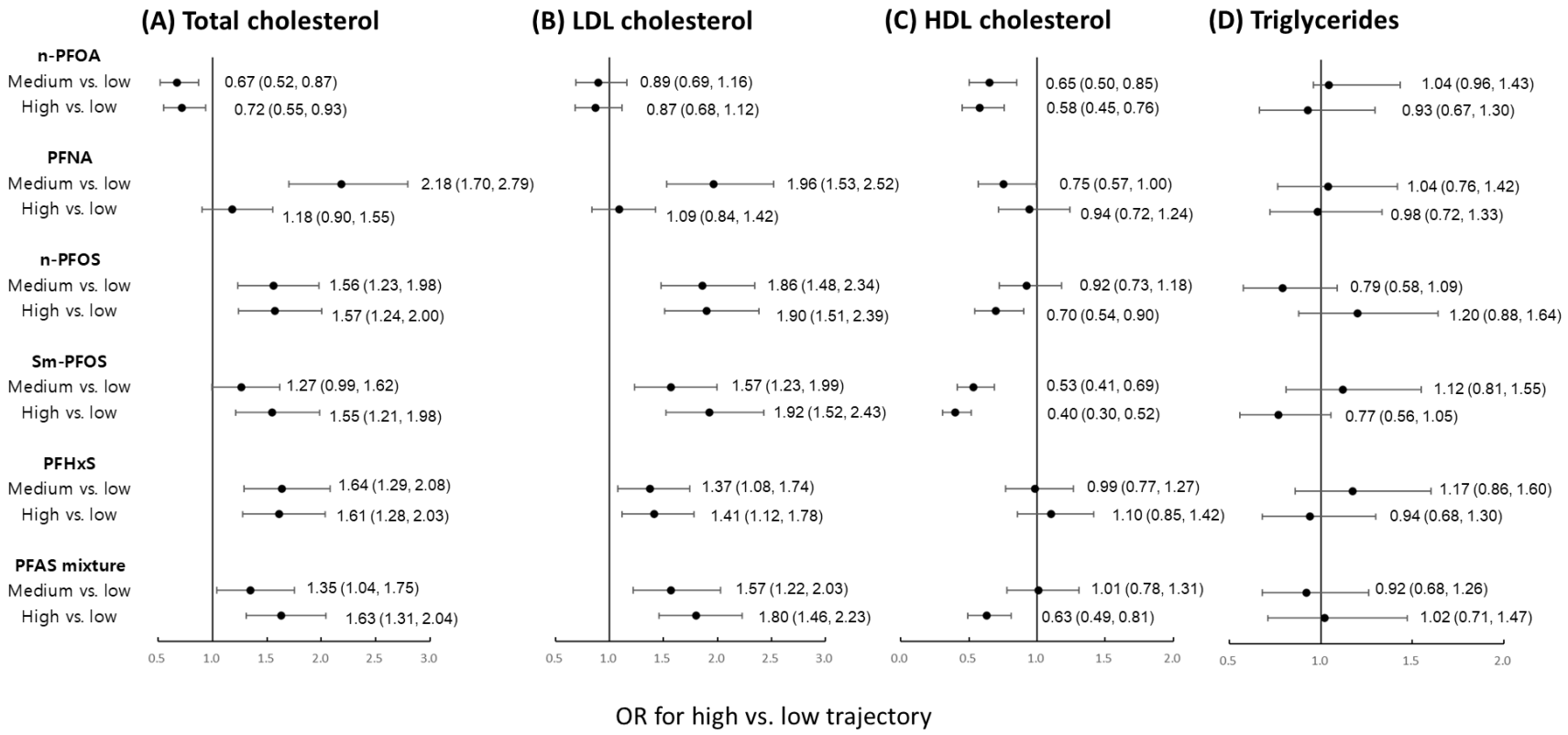

Figure S3. Odds ratios (●) and their 95% confidence intervals (bar) for associations of tertiles of PFAS concentrations (versus tertile 1) or PFAS mixture (versus low concentration) with trajectories (high versus low trajectories) of (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, and (D) triglycerides when the models were not adjusted for BMI in the SWAN-MPS cohort (1999–2016, n = 1130). The models were adjusted for site × race/ethnicity, age, education, menopausal status, smoking status, alcohol consumption, physical activity, and total energy intake. The numbers at the right side of the bars represent odds ratios and their 95% confidence intervals. Results with continuous PFAS concentrations can be found in supplemental Table S14.

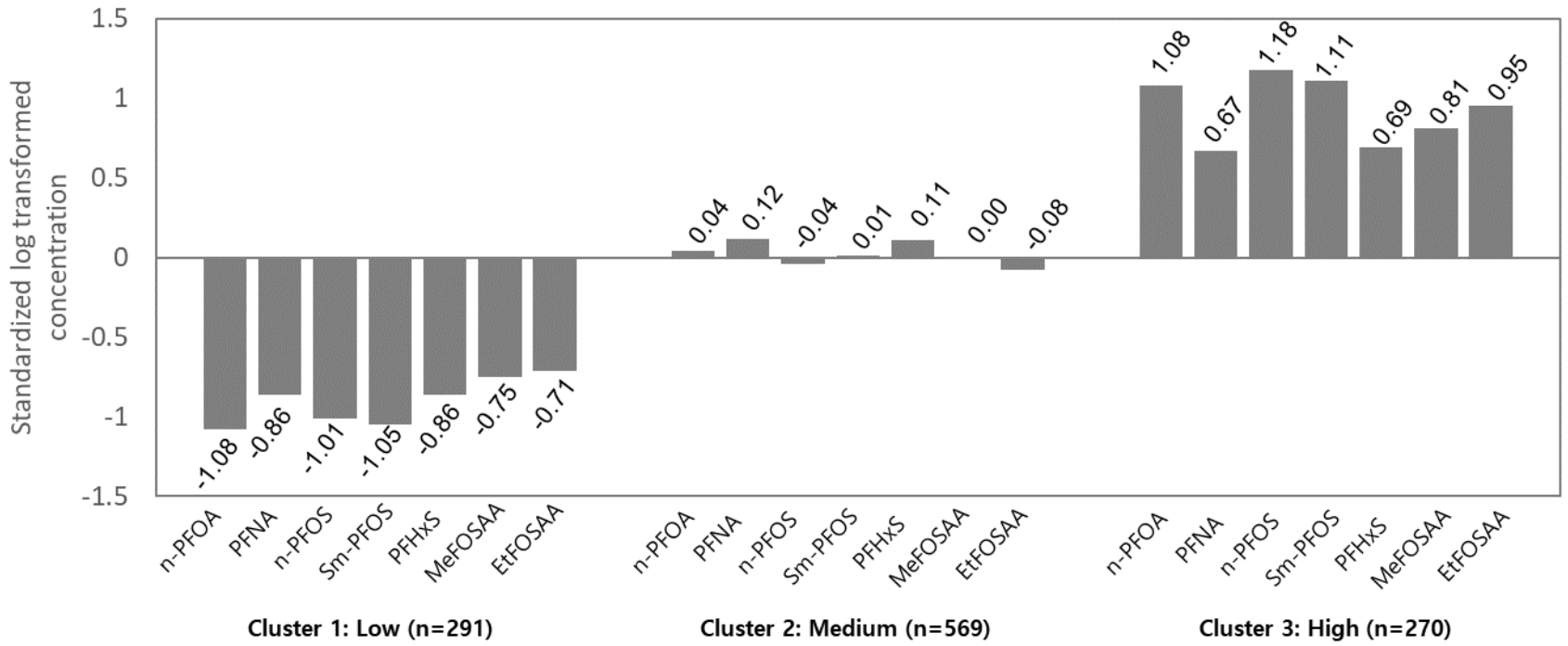

Figure S4. Means of the standardized log-transformed serum PFAS concentrations in each cluster identified by k-means clustering in the SWAN-MPS cohort (1999–2016, n = 1130). Cluster 1 (n=291): "low" overall PFAS concentration pattern; clusters 2 (n=569): "medium" overall PFAS concentration pattern; cluster 3 (n=270): "high" overall PFAS concentration pattern.

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