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Supplemental Material

Plasma Concentrations of Perfluoroalkyl Substances and Risk of Type 2 Diabetes: A Prospective Investigation among U.S. Women

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Table S1. Concentrations and detection rate of minor PFASs by T2D status in the Nurses' Health Study II.

PFASs	T2D cases (n=793)		T2D controls (n=793)		
	Detection rate %	Median (IQR)	Detection rate %	Median (IQR)	
PFHxA	27%	0.02(0.02, 0.04)	26%	0.02(0.02, 0.04)	0.85
PFHpA	70%	0.09(0.02, 0.22)	63%	0.06(0.02, 0.17)	<0.001
PFUnDA	85%	0.08(0.04, 0.13)	89%	0.10(0.06, 0.18)	<0.001
PFDoDA	21%	0.02(0.02, 0.02)	23%	0.02(0.02, 0.02)	0.26
PFHpS	99%	0.72(0.47, 0.98)	99%	0.61(0.38, 0.92)	<0.001
N-MeFOSAA	100%	1.50(1.04, 2.39)	100%	1.55(0.98, 2.37)	0.82
N-EtFOSAA	100%	1.94(1.14, 3.70)	100%	1.74(1.02, 3.25)	0.009
Total FOSA	98%	0.50(0.22, 1.26)	99%	0.53(0.24, 1.25)	0.36

Abbreviations: PFHxA, perfluorohexanoic acid; PFHpA, Perfluoroheptanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluorododecanoic acid; PFHpS ,Perfluoroheptane sulfonate; N-MeFOSAA, N-methyl perfluorooctane sulfonamide; N-EtFOSAA, N-ethyl perfluorooctanesulfonamidoacetic acid; FOSA, Perfluorooctanesulfonamide.

Table S2. Partial Spearman correlation coefficients between PFASs and intake of individual foods among controls (n=793).

	PFOS	PFOA	PFHxS	PFNA	PFDA
Apple juice or cider	0.01	-0.01	-0.03	-0.004	0.02
Avocado	-0.04	-0.05	-0.03	-0.03	-0.05
Bacon	0.11	0.01	-0.02	0.07	0.01
Bananas	-0.04	-0.04	-0.02	-0.06	-0.04
Beans or lentils	-0.07	-0.04	-0.04	-0.09	-0.03
Beef or lamb as main dish	0.09	0.02	0.03	0.08	0.08
Beef/pork/lamb as a Sandwich	0.04	-0.01	-0.04	-0.01	0.03
Beer	-0.04	-0.04	-0.07	-0.02	-0.05
Beets	-0.07	-0.07	0.01	0.01	0.01
Blueberries	0.05	0.02	0.02	0.12	0.13
Broccoli	-0.02	0.01	-0.06	0.03	0.01
Brown rice	-0.01	0.0004	0.03	-0.004	0.01
Brownies	0.08	0.07	-0.003	0.04	-0.0001
Brussels sprouts	-0.06	-0.04	-0.04	0.06	0.05
Caffeine free coke, Pepsi	0.04	0.005	-0.03	-0.05	-0.06
Cake, home-baked	-0.002	-0.01	-0.06	-0.003	0.02
Cake, ready-made	0.03	0.05	0.03	0.09	0.12
Candy bars	0.09	0.10	-0.02	0.02	0.02
Candy bars with chocolate	0.003	0.04	0.03	0.11	0.06
Candy without chocolate	0.04	0.05	0.04	-0.04	0.01
Canned tuna	-0.04	-0.06	0.02	0.02	-0.06
Cantaloupe	0.11	0.07	0.04	0.12	0.13
Cauliflower	-0.07	0.02	-0.04	-0.03	-0.03
Celery	0.0005	0.02	0.08	-0.04	-0.03
Chicken, with skin	0.04	-0.03	-0.04	0.04	0.05
Chocolate bars	0.10	0.08	0.01	0.003	0.001
Chowder or cream soup	0.03	-0.01	-0.02	0.02	0.04
Coffee	0.01	-0.01	0.05	-0.04	-0.01
Coke, Pepsi, other colas	-0.03	-0.01	0.01	-0.02	-0.03
Cold breakfast cereal	-0.03	-0.01	-0.04	-0.04	-0.02
Coleslaw, cabbage	-0.01	0.05	-0.01	0.01	0.03
Cooked carrots or juice	0.02	-0.004	0.02	0.05	0.05
Cooked oatmeal/oat bran	0.002	0.02	0.03	-0.002	-0.03
Cookies, home-baked	-0.003	-0.08	-0.05	-0.03	-0.03
Cookies, ready-made	0.001	0.05	0.02	-0.001	0.02
Corn	0.08	0.02	-0.03	0.05	0.07
Crackers	0.04	0.02	0.03	0.04	-0.01
Dark bread	-0.05	-0.02	0.02	-0.08	-0.02
Dark meat fish	-0.01	-0.01	0.05	0.12	0.10
Decaffeinated coffee	-0.03	0.01	0.01	-0.10	-0.02
Doughnuts	0.02	0.02	0.03	0.02	0.02
Eggplant, zucchini	-0.004	-0.02	-0.02	0.08	0.10
Eggs	0.03	-0.03	-0.03	-0.02	-0.04
English muffins/bagels/rolls	-0.05	-0.03	-0.04	0.03	0.01
French fried potatoes	0.11	0.04	0.03	0.06	0.01

Fresh apples or pears	-0.02	-0.03	0.05	-0.04	-0.04
Garlic	0.004	-0.04	0.01	0.05	0.05
Grapefruit	0.01	0.04	0.02	0.06	0.05
Grapefruit juice	-0.03	-0.02	-0.02	0.06	0.05
Green peppers	0.02	0.03	0.06	0.09	0.04
Kale/mustard/chard	-0.03	-0.01	0.02	0.08	0.01
Hamburger	0.05	-0.01	-0.04	0.01	-0.02
Hawaiian punch	0.01	-0.07	-0.05	-0.07	-0.05
Hot dogs	0.04	-0.04	0.03	0.002	0.02
Iceberg or head lettuce	0.02	0.05	0.13	-0.02	-0.003
Jams, jellies	-0.04	0.05	0.06	0.03	0.02
Light beer	-0.05	-0.09	-0.07	-0.06	0.003
Liquor	-0.04	0.003	0.02	-0.02	-0.04
Low calorie caffeine-free cola	0.04	0.04	0.05	0.03	0.01
Low calorie cola	-0.01	0.05	0.02	0.04	0.01
Mayonnaise	0.06	0.05	0.03	0.01	0.002
Mixed vegetables	0.04	-0.002	0.02	0.03	0.02
Muffins or biscuits	0.07	0.02	-0.01	0.07	0.08
Oat bran	-0.01	0.004	-0.03	-0.04	0.02
Oil and vinegar dressing	-0.03	-0.05	0.03	-0.02	-0.02
Olive oil dressing	0.0004	-0.01	-0.004	-0.01	-0.01
Onion as a garnish	0.07	0.02	0.05	-0.01	0.01
Onion as a vegetable	0.04	0.02	0.03	0.07	0.03
Orange juice	-0.004	0.03	0.01	-0.03	-0.05
Orange squash	-0.003	-0.04	-0.02	0.04	0.06
Oranges	0.07	0.05	0.05	0.002	0.04
Other carbonated beverage with sugar	-0.02	-0.02	-0.04	-0.07	-0.02
Other low calorie carbonated beverage	0.02	0.02	-0.005	0.02	-0.002
Other bran	-0.01	0.02	0.01	-0.02	0.03
Other cooked breakfast cereal	-0.01	-0.004	0.01	-0.02	-0.03
Other fish	0.07	0.04	0.08	**0.16**[a]	**0.19**[a]
Other fruit juices	0.02	-0.02	0.04	-0.05	-0.05
Other grains	-0.07	-0.06	0.01	-0.05	-0.04
Other nuts	-0.05	-0.03	-0.05	-0.08	-0.08
Pancakes or Waffles	-0.04	-0.03	-0.05	-0.06	-0.01
Pasta	-0.05	-0.05	-0.05	0.02	0.02
Peach, apricots, plums	0.02	0.02	0.02	0.04	0.06
Peanut butter	-0.03	-0.04	-0.09	-0.13	-0.08
Peanuts	0.04	-0.03	-0.04	-0.06	-0.07
Peas, or lima beans	-0.11	-0.06	-0.05	-0.06	-0.04
Pie, home-baked	0.001	-0.08	-0.03	0.03	0.05
Pie, ready-made	0.04	-0.02	0.03	0.02	0.05
Pizza	0.04	0.01	-0.03	-0.03	-0.03
Plain water	0.01	0.05	0.03	0.01	0.01
Popcorn	**0.29**[a]	0.13	-0.04	-0.04	-0.02
Pork as a main dish	0.06	0.01	0.06	0.10	0.09
Potato/corn chips	0.07	0.003	-0.02	-0.04	-0.06
Baked/boiled/mashed potatoes	0.05	0.02	-0.01	0.02	0.05

Processed meats	-0.01	-0.03	-0.05	0.01	0.01
Prunes	-0.08	-0.06	-0.04	-0.07	-0.04
Raisins	-0.02	-0.03	-0.02	-0.01	0.03
Raw carrots	-0.002	0.02	0.06	-0.09	-0.07
Red chili sauce	0.002	-0.01	0.01	-0.01	-0.03
Red wine	0.01	-0.02	-0.03	-0.03	0.03
Romaine or leaf lettuce	-0.02	-0.04	0.03	0.01	0.05
Shrimp, lobster, scallops	0.08	0.04	0.08	**0.24**[a]	**0.24**[a]
Spinach, cooked	0.05	0.04	0.04	0.13	0.14
Spinach, raw	0.01	0.01	0.05	0.05	0.06
Strawberries	0.04	0.02	0.01	0.07	0.04
String beans	0.01	0.05	0.02	0.06	0.03
Sweet roll, homemade	0.07	0.03	0.08	0.09	0.07
Sweet roll, ready made	0.04	0.05	-0.02	0.06	0.06
Tea	0.04	0.05	0.10	0.10	0.05
Tofu or Soybeans	0.01	0.04	0.05	-0.01	0.01
Tomato juice	0.05	0.07	0.04	0.04	-0.02
Tomato sauce	-0.04	-0.003	-0.01	-0.01	0.002
Tomatoes	-0.02	-0.02	0.04	0.01	0.05
Tortillas	-0.03	-0.06	-0.03	-0.09	-0.08
Total coffee	-0.01	-0.003	0.04	-0.07	-0.01
Turkey, including ground Dogs	0.01	0.02	0.05	0.01	0.05
Wheat germ	-0.01	-0.02	-0.05	-0.05	-0.01
White bread	0.02	-0.02	0.004	0.07	0.04
White rice	0.03	0.0001	0.03	0.11	0.10
White wine	-0.003	-0.04	0.03	0.07	0.08
Yams or sweet potatoes	0.02	-0.04	-0.002	0.10	0.10
Yogurt	-0.02	-0.02	0.04	-0.02	0.03

Partial spearman correlation was calculated after adjustment of age at blood draw(in years), ethnicity (white, or others), time of blood draw (Mar-May, Jun-Aug, Sep-Nov, and Dec-Feb), fasting status (yes, or no), family history of diabetes (yes, or no), menopausal status and post-menopausal hormone use (pre-menopause, post-menopause and never use hormone, post-menopause and former or current use hormone, or missing), oral contraceptive use (never used, past user, or current user), states of residence (coastal, lake, or inland), breastfeeding duration (Nulliparous or parous without breastfeeding, ≤11 months, or ≥12 months), number of children delivery after 1993 (0, 1,or ≥2), smoking status (never, former, or current), alcohol intake (abstainer, <5.0 g/day, 5.0-14.9 g/day, or ≥15.0 g/day), physical activity (METs-hr/week, <3, 3-8.9, 9-17.9, 18-26.9, or ≥27), baseline BMI (kg/m^2, <23.0, 23.0–24.9, 25.0-29.9, 30.0-34.9, or ≥ 35.0) and calorie intake.

[a] P<0.05 after Bonferroni correction.

Table S3. Partial Pearson correlation coefficients of PFASs with total adiponectin, insulin, HbA1c, and blood lipids among controls.

	PFOS	P value	PFOA	P value	PFHxS	P value	PFNA	P value	PFDA	P value
PFOA	0.58	<0.001								
PFHxS	0.31	<0.001	0.32	<0.001						
PFNA	0.43	<0.001	0.37	<0.001	0.27	<0.001				
PFDA	0.39	<0.001	0.25	<0.001	0.20	<0.001	0.67	<0.001		
Total adiponectin	-0.04	0.25	-0.05	0.21	0.05	0.20	-0.001	0.99	0.08	0.03
HbA1c	0.04	0.28	0.03	0.40	-0.03	0.41	0.01	0.79	-0.02	0.55
Total lipids	0.07	0.06	0.10	0.005	0.003	0.93	0.08	0.04	0.04	0.26
Cholesterol	0.10	0.006	0.10	0.006	0.02	0.51	0.13	<0.001	0.14	<0.001
triglycerides	0.001	0.97	0.05	0.14	-0.02	0.62	-0.04	0.25	-0.10	0.005
Insulin	0.04	0.40	-0.003	0.95	-0.02	0.62	-0.001	0.97	-0.06	0.16

Number of participants were 793, except n=792 for adiponectin, 751 for HbA1c, and 546 for fasting insulin. Partial spearman correlation was calculated after adjustment of age at blood draw(in years), ethnicity (white, or others), time of blood draw (Mar-May, Jun-Aug, Sep-Nov, and Dec-Feb), fasting status (yes, or no), family history of diabetes (yes, or no), menopausal status and post-menopausal hormone use (pre-menopause, post-menopause and never use hormone, post-menopause and former or current use hormone, or missing), oral contraceptive use (never used, past user, or current user), states of residence (coastal, lake, or inland), breastfeeding duration (Nulliparous or parous without breastfeeding, ≤11 months, or ≥12 months), number of children delivery after 1993 (0, 1,or ≥2), smoking status (never, former, or current), alcohol intake (abstainer, <5.0 g/day, 5.0-14.9 g/day, or ≥15.0 g/day), physical activity (METs-hr/week, <3, 3-8.9, 9-17.9, 18-26.9, or ≥27), baseline BMI (kg/m^2, <23.0, 23.0–24.9, 25.0-29.9, 30.0-34.9, or ≥ 35.0), and AHEI score (in quintiles).

Table S4. Associations between original PFAS concentrations and risk of T2D after deleting batches with within-batch CVs for any PFASs >20% (n=1,066).

Exposure	Range (median) ng/mL	Cases (n)	Controls (n)	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
PFOS					
Tertile 1	(6.04–26.3) 19.7	133	178	Ref	Ref
Tertile 2	(26.3–41.4) 33.1	189	178	1.46 (1.05, 2.01)	1.65 (1.01, 2.72)
Tertile 3	(41.4–421) 56.3	210	178	1.62 (1.18, 2.23)	2.04 (1.24, 3.36)
P-trend[c]	--	--	--	0.004	0.006
Log_{10} PFOS[d]	--	--	--	1.17 (1.03, 1.33)	1.27 (1.03, 1.56)
P-value[e]	--	--	--	0.02	0.03
PFOA					
Tertile 1	(0.99–3.76) 2.89	157	178	Ref	Ref
Tertile 2	(3.76–5.48) 4.57	168	178	1.05 (0.77, 1.43)	0.95 (0.59, 1.54)
Tertile 3	(5.48–112) 7.36	207	178	1.30 (0.96, 1.77)	1.63 (0.99, 2.69)
P-trend[c]	--	--	--	0.08	0.04
Log_{10} PFOS[d]	--	--	--	1.15 (1.01, 1.32)	1.23 (1.01, 1.50)
P-value[e]	--	--	--	0.03	0.04
PFHxS					
Tertile 1	(0.32–1.49) 1.09	166	178	Ref	Ref
Tertile 2	(1.49–2.90) 2.01	185	178	1.11 (0.82, 1.50)	1.19 (0.77, 1.86)
Tertile 3	(2.91–429) 4.77	181	178	1.09 (0.81, 1.48)	1.24 (0.78, 1.98)
P-trend[c]	--	--	--	0.58	0.38
Log_{10} PFOS[d]	--	--	--	1.06 (0.94, 1.20)	1.03 (0.86, 1.24)
P-value[e]	--	--	--	0.33	0.75
PFNA					
Tertile 1	(0.09–0.47) 0.37	184	178	Ref	Ref
Tertile 2	(0.47–0.77) 0.61	204	178	1.09 (0.81, 1.48)	1.09 (0.68, 1.72)
Tertile 3	(0.77–7.74) 1.05	144	178	0.75 (0.54, 1.05)	0.87 (0.53, 1.43)
P-trend[c]	--	--	--	0.09	0.58
Log_{10} PFOS[d]	--	--	--	0.97 (0.85, 1.10)	1.03 (0.84, 1.26)
P-value[e]	--	--	--	0.63	0.79
PFDA					
Tertile 1	(0.01–0.13) 0.09	281	178	Ref	Ref
Tertile 2	(0.13–0.20) 0.16	160	178	0.58 (0.44, 0.77)	0.83 (0.54, 1.29)
Tertile 3	(0.20–1.95) 0.27	91	178	0.31 (0.22, 0.44)	0.56 (0.34, 0.92)
P-trend[c]	--	--	--	<0.001	0.02
Log_{10} PFOS[d]	--	--	--	0.63 (0.55, 0.73)	0.82 (0.67, 1.00)
P-value[e]	--	--	--	<0.001	0.05

Odds ratios according to batch-corrected PFAS tertiles were estimated using conditional logistic regression;

[a] Model 1, conditioned on matching factors, including age, month of sample collection, fasting status, menopausal status and post-menopausal hormone use (pre-menopause, post-menopause and never use hormone, post-menopause and former or current use hormone, or missing);

[b] Model 2, further adjusted for family history of diabetes (yes, or no), oral contraceptive use (never used, past user, or current user), breastfeeding duration at blood draw (nulliparous or parous without breastfeeding, ≤11 months, or ≥12 months) and number of children delivered after 1993 (0, 1,or ≥2), states of residence (coastal, the Great Lake region, or inland), smoking status (never, former, or current), alcohol intake (abstainer, <5.0 g/day, 5.0-14.9 g/day, or ≥15.0 g/day), physical activity

(METs-hr/week, <3, 3-8.9, 9-17.9, 18-26.9, or ≥27), baseline BMI (kg/m^2, <23.0, 23.0–24.9, 25.0-29.9, 30.0-34.9, or ≥ 35.0), and AHEI score (in quintiles).

[c] P values for trend were calculated by analyzing median PFAS values in each category as a continuous variable.

[d] ORs for a 1-SD increase in log10-transformed PFASs, which were 0.2286269 for PFOS, 0.2496809 for PFOA, 0.3444994 for PFHxS, 0.2544009 for PFNA, 0.3080753 for PFDA.

Table S5. The association between PFAS concentrations and T2D stratified by duration of follow-up (n=1586).

		Tertile 1	Tertile 2	Tertile 3	P_{trend}	$P_{interaction}$
	Time of T2D diagnosis					
PFOS	No later than 2005	Ref	1.49 (0.96, 2.33)	1.62 (1.04, 2.54)	0.04	0.70
	After 2005	Ref	1.37 (0.86, 2.19)	1.29 (0.81, 2.07)	0.33	
PFOA	No later than 2005	Ref	1.22 (0.78, 1.90)	1.22 (0.78, 1.89)	0.41	0.77
	After 2005	Ref	1.15 (0.73, 1.82)	1.44 (0.90, 2.31)	0.12	
PFHxS	No later than 2005	Ref	1.25 (0.83, 1.90)	1.15 (0.73, 1.80)	0.53	0.96
	After 2005	Ref	1.10 (0.70, 1.75)	0.97 (0.60, 1.56)	0.84	
PFNA	No later than 2005	Ref	0.65 (0.43, 0.98)	0.67 (0.42, 1.06)	0.05	0.24
	After 2005	Ref	1.00 (0.64, 1.55)	0.70 (0.44, 1.11)	0.13	
PFDA	No later than 2005	Ref	0.97 (0.62, 1.51)	1.06 (0.68, 1.64)	0.76	0.79
	After 2005	Ref	1.01 (0.65, 1.58)	0.94 (0.59, 1.48)	0.76	
	AHEI					
PFOS	≤48	Ref	1.28 (0.82, 2.00)	1.45 (0.92, 2.28)	0.11	0.62
	>48	Ref	1.80 (1.13, 2.88)	1.68 (1.06, 2.67)	0.04	
PFOA	≤48	Ref	0.92 (0.59, 1.44)	1.36 (0.86, 2.16)	0.16	0.29
	>48	Ref	1.44 (0.91, 2.30)	1.57 (0.98, 2.50)	0.07	
PFHxS	≤48	Ref	1.72 (1.10, 2.69)	1.37 (0.86, 2.18)	0.23	0.82
	>48	Ref	1.91 (1.20, 3.03)	1.65 (1.04, 2.64)	0.05	
PFNA	≤48	Ref	0.86 (0.57, 1.30)	0.67 (0.42, 1.07)	0.10	0.53
	>48	Ref	0.80 (0.52, 1.25)	0.92 (0.58, 1.45)	0.69	
PFDA	≤48	Ref	1.05 (0.68, 1.64)	0.97 (0.61, 1.54)	0.87	0.98
	>48	Ref	1.04 (0.66, 1.63)	1.08 (0.69, 1.68)	0.74	

Odds ratios were estimated using conditional logistic regression based on model 2 in Table 3. P values for trend were performed by median PFAS values in each categorical as a continuous variable. Statistical significance of effect modification (P for interaction) was evaluated by LRT comparing models with and without interaction terms between tertiles of PFAS concentrations and the effect modifiers.