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Supplemental Material

Plasma Concentrations of Per- and Polyfluoroalkyl Substances at Baseline and Associations with Glycemic Indicators and Diabetes Incidence among High-Risk Adults in the Diabetes Prevention Program Trial

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Figure S1. PFAS geometric means in the Diabetes Prevention Program (red) and six NHANES cycles (blue colors)

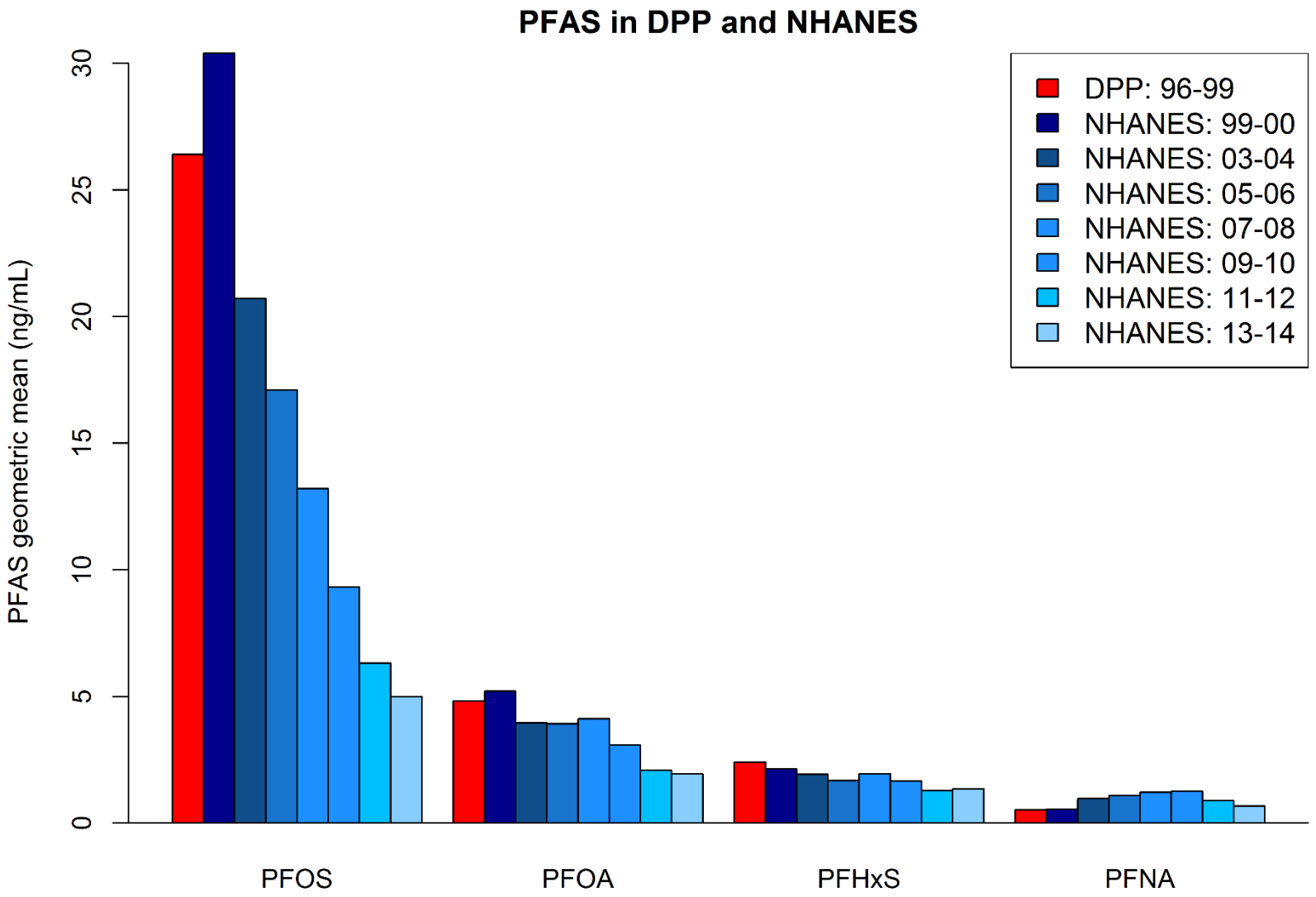

Table S1. PFAS geometric means and 95% CIs (ng/mL) in NHANES and in the Diabetes Prevention Program (DPP)

NHANES/DPP Survey year	PFOS	PFOA	PFHxS	PFNA	Et-PFOSA-AcOH	Me-PFOSA-AcOH
DPP (1996-1999)	**26.4 (25.3-27.5)**	**4.82 (4.65-5.00)**	**2.41 (2.29-2.54)**	**0.53 (0.50-0.56)**	**1.13 (1.06-1.21)**	**0.94 (0.89-1.00)**
1999-2000	30.4 (27.1-33.9)	5.21 (4.72-5.74)	2.13 (1.91-2.38)	0.55 (0.46-0.67)	0.64 (0.59-0.69)	0.84 (0.73-0.97)
2003-2004	20.7 (19.2-22.3)	3.95 (3.65-4.27)	1.93 (1.73-2.16)	0.97 (0.82-1.14)	<LOD	<LOD
2005-2006	17.1 (16.0-18.2)	3.92 (3.48-4.42)	1.67 (1.42-1.98)	1.09 (0.91-1.29)	<LOD	0.41 (0.37-0.45)
2007-2008	13.2 (12.2-14.2)	4.12 (4.01-4.24)	1.95 (1.76-2.17)	1.22 (1.12-1.32)	<LOD	0.30 (0.27-0.33)
2009-2010	9.32 (8.13-10.7)	3.07 (2.81-3.36)	1.66 (1.51-1.82)	1.26 (1.11-1.44)	<LOD	0.19 (0.18-0.21)
2011-2012	6.31 (5.84-6.82)	2.08 (1.95-2.22)	1.28 (1.15-1.43)	0.88 (0.80-0.97)	<LOD	<LOD
2013-2014	4.99 (4.50-5.52)	1.94 (1.76-2.14)	1.35 (1.20-1.52)	0.67 (0.61-0.74)	---	<LOD

Table S2. [a]Adjusted cross-sectional associations between baseline PFAS plasma concentrations and glycemic outcomes in the Diabetes Prevention Program among isomers of PFOS (n-PFOS, Sm-PFOS, Sm2-PFOS) and PFOA (n-PFOA and Sb-PFOA) and PFOA (n-PFOA, Sb-PFOA)

Outcome	**n**	**Mean (SD)**	**β Coefficient (95% CI)** Per doubling in PFASs concentration (ng/ml)				
			n-PFOS	**Sm-PFOS**	**Sm2-PFOS**	**n-PFOA**	**Sb-PFOA**
HOMA-IR	956	6.91 (3.9)	**0.31 (0.05, 0.56)** *P*=0.02	**0.48 (0.23, 0.73)** *P*=1.79x10^{-4}	0.14 (-0.06, 0.34) *P*=0.17	**0.64 (0.33, 0.96)** *P*=6.10x10^{-5}	**0.34 (0.18, 0.51)** *P*=4.87x10^{-5}
Fast. Insulin (µU/mL)	956	26 (14.6)	**1.06 (0.13, 1.99)** *P*=0.03	**1.73 (0.82, 2.64)** *P*=2.02x10^{-4}	0.50 (-0.23, 1.23) *P*=0.18	**2.29 (1.15, 3.43)** *P*=9.13x10^{-5}	**1.16 (0.56, 1.76)** *P*=1.63x10^{-4}
30-min insulin (µU/mL)	945	96.5 (53.6)	2.98 (-0.60, 6.56) *P*=0.10	**6.53 (3.00, 10.06)** *P*=3.02x10^{-4}	2.13 (-0.70, 1.23) *P*=0.14	**8.11 (3.70, 12.51)** *P*=3.19x10^{-4}	**3.41 (1.09, 5.74)** *P*=4.06x10^{-3}
Fast. proinsulin (pM)	954	17.9 (13)	**1.22 (0.38, 2.06)** *P*=4.42x10^{-3}	**1.24 (0.42, 2.06)** *P*=3.22x10^{-3}	0.53 (-0.13, 1.19) *P*=0.11	**1.78 (0.75, 2.82)** *P*=7.65x10^{-4}	**0.76 (0.21, 1.30)** *P*=6.33x10^{-3}
HOMA-β	956	217 (120)	6.83 (-0.92, 14.58) *P*=0.08	**13.06 (5.47, 20.65)** *P*=7.62x10^{-4}	3.93 (-2.16, 10.02) *P*=0.21	**16.6 (7.05, 26.15)** *P*=6.73x10^{-4}	**7.25 (2.24, 12.27)** *P*=4.64x10^{-3}
Corrected insulin response	945	0.60 (0.39)	0.02 (-0.01, 0.04) *P*=0.23	**0.04 (0.01, 0.07)** *P*=2.56x10^{-3}	0.01 (-0.01, 0.03) *P*=0.21	**0.04 (0.01, 0.07)** *P*=0.01	0.02 (-0.001, 0.03) *P*=0.07
Insulinogenic index	945	1.03 (0.84)	0.03 (-0.03, 0.09) *P*=0.28	**0.08 (0.03, 0.14)** *P*=3.84x10^{-3}	0.04 (-0.01, 0.08) *P*=0.11	**0.08 (0.01, 0.15)** *P*=0.02	0.03 (-0.01, 0.07**)** *P*=0.09
Fast. Glucose (mg/dL)	957	106.9 (7.4)	**0.55 (0.05, 1.04)** *P*=0.03	0.47 (-0.01, 0.96) *P*=0.06	0.26 (0.12, 0.65) *P*=0.18	0.259 (-0.02, 1.20) *P*=0.06	**0.50 (0.18, 0.82)** *P*=2.27x10^{-3}

30-min glucose (mg/dL)	947	170.2 (24.3)	0.69 (-0.94, 2.23) *P*=0.41	0.51 (-1.10, 2.13) *P*=0.53	0.44 (-0.85, 1.73) *P*=0.50	1.55 (-0.47, 3.57) *P*=0.13	1.04 (-0.02, 2.11) *P*=0.05
2-hour glucose (mg/dL)	940	164.6 (17)	0.03 (-1.13, 1.19) *P*=0.96	0.03 (-1.13, 1.19) *P*=0.96	-0.17 (-1.08, 0.74) *P*=0.71	-0.53 (-1.97, 0.90) *P*=0.47	-0.02 (-0.77, 0.74) *P*=0.96
HbA1C (%)	954	5.9 (0.5)	**0.55 (0.05, 1.04)** *P*=0.03	0.02 (-0.01, 0.06) *P*=0.12	0.02 (-0.01, 0.04) *P*=0.19	**0.05 (0.001, 0.08)** *P*=0.04	0.01 (-0.01, 0.03) *P*=0.26
Adiponectin (µg/mL)	956	8.1 (3.5)	-0.09 (-0.30, 0.12) *P*=0.42	-0.15 (-0.35, 0.06) *P*=0.17	-0.15 (-0.35, 0.06) *P*=0.17	-0.25 (-0.51, 0.01) *P*=0.06	**-0.26 (-0.40, -0.13)** $P=1.56x10^{-4}$
†BMI	957	32.6 (6.6)	0.21 (-0.21, 0.63**)** *P*=0.33	0.32 (-0.09, 0.74**)** *P*=0.13	-0.21 (-0.54, 0.13**)** *P*=0.22	0.15 (-0.37, 0.67**)** *P*=0.58	0.09 (-0.18, 0.37**)** *P*=0.52

[a]Adjusted for participant sex, race/ethnicity, BMI (continuous), age (categorical), marital status (categorical), education (categorical), and smoking history (categorical)

†Not adjusted for BMI

Table S3. Adjusted longitudinal associations of baseline plasma PFAS concentrations and prospective metabolic and glycemic measurements in the DPP.

PFAS Analyte	**HOMA-IR**		
	Model 1	Model 2	Model 3
$\log_2$-PFAS	$\boldsymbol{\beta(PFAS * time)}$ **Est. (95% CI)**	$\boldsymbol{\beta(PFAS * Tx)}$ **Est. (95% CI)**	$\boldsymbol{\beta(PFAS * time * Tx)}$ **Est. (95% CI)**
PFOS	-0.04 (-0.15, 0.07) *P*=0.50	0.17 (-0.26, 0.61) *P*=0.44	0.02 (-0.20, 0.25) *P*=0.86
PFOA	0.02 (-0.11, 0.14) *P*=0.82	0.08 (-0.41, 0.57) *P*=0.76	-0.01 (-0.27, 0.24) *P*=0.94
PFHxS	0.01 (-0.06, 0.10) *P*=0.67	-0.06 (-0.53, 0.11) *P*=0.74	-0.09 (-0.26, 0.08) *P*=0.30
Et-PFOSA-AcOH	-0.02 (-0.09, 0.05) *P*=0.56	-0.01 (-0.53, 0.11) *P*=0.92	0.03 (-0.11, 0.18) *P*=0.65
Me-PFOSA-AcOH	0.04 (-0.03, 0.13) *P*=0.24	-0.21 (-0.53, 0.11) *P*=0.21	-0.002 (-0.17, 0.16) *P*=0.97
PFNA	0.06 (-0.03, 0.14) *P*=0.18	0.01 (-0.33, 0.35) *P*=0.96	-0.06 (-0.23, 0.11) *P*=0.48
	HOMA-β		
PFOS	-1.12 (-4.01, 1.76) *P*=0.45	8.65 (-3.46, 20.76) *P*=0.16	0.67 (-5.11, 6.44) *P*=0.82
PFOA	-1.50 (-4.76, 1.76) *P*=0.37	0.06 (-13.65, 13.77) *P*=0.99	-0.12 (-6.64, 6.40) *P*=0.97
PFHxS	0.55 (-1.58, 2.68) *P*=0.61	-5.02 (-14.42, 4.38) *P*=0.29	-0.38 (-4.68, 3.91) *P*=0.86
Et-PFOSA-AcOH	**-1.96 (-3.81, -0.11) *P*=0.04**	1.34 (-6.33, 9.01) *P*=0.73	0.46 (-3.24, 4.16) *P*=0.81
Me-PFOSA-AcOH	-0.51 (-2.63, 1.61) *P*=0.64	-0.81 (-9.81, 8.19) *P*=0.86	0.73 (-3.51, 4.96) *P*=0.74
PFNA	1.26 (-0.91, 3.42) *P*=0.25	0.36 (-9.03, 9.75) *P*=0.94	-2.65 (-6.99, 1.68) *P*=0.23
	Fast. Insulin (μU/mL)		
PFOS	-0.14 (-0.50, 0.22) *P*=0.43	0.78 (-0.69, 2.25) *P*=0.30	-0.06 (-0.87, 0.75) *P*=0.89
PFOA	-0.01 (-0.42, 0.40) *P*=0.96	0.13 (-1.53, 1.78) *P*=0.88	0.11 (-0.61, 0.82) *P*=0.77
PFHxS	0.06 (-0.20, 0.33) *P*=0.63	-0.45 (-1.59, 0.69) *P*=0.44	-0.22 (-0.76, 0.31) *P*=0.42
Et-PFOSA-AcOH	-0.13 (-0.37, 0.10) *P*=0.25	0.05 (-0.87, 0.98) *P*=0.91	0.12 (-0.34, 0.58) *P*=0.60
Me-PFOSA-AcOH	0.10 (-0.16, 0.36) *P*=0.47	-0.61 (-1.69, 0.48) *P*=0.27	0.01 (-0.52, 0.54) *P*=0.97
PFNA	0.19 (-0.08, 0.46) *P*=0.16	0.001 (-1.13, 1.14) *P*=0.99	-0.26 (-0.80, 0.28) *P*=0.34

Table S3 continued.

PFAS Analyte	Fasting Glucose (mg/dL)		
	Model 1	Model 2	Model 3
log_2-PFAS	$\boldsymbol{\beta(PFAS * time)}$ **Est. (95% CI)**	$\boldsymbol{\beta(PFAS * Tx)}$ **Est. (95% CI)**	$\boldsymbol{\beta(PFAS * time * Tx)}$† **Est. (95% CI)**
PFOS	-0.10 (-0.35, 0.19) *P*=0.56	-0.79 (-1.90, 0.33) *P*=0.16	0.09 (-0.53, 0.71) *P*=0.79
PFOA	0.14 (-0.17, 0.45) *P*=0.38	-0.15 (-1.41, 1.11) *P*=0.82	-0.19 (-0.73, 0.35) *P*=0.49
PFHxS	-0.02 (-0.23, 0.19) *P*=0.86	0.26 (-0.37, 1.36) *P*=0.26	**-0.42 (-0.84, -0.01) *P*=0.04**
Et-PFOSA-AcOH	0.09 (-0.07, 0.27) *P*=0.28	-0.49 (-1.19, 0.22) *P*=0.17	0.03 (-0.32, 0.37) *P*=0.88
Me-PFOSA-AcOH	0.17 (-0.03, 0.37) *P*=0.09	-0.76 (-1.59, 0.206) *P*=0.07	-0.03 (-0.43, 0.38) *P*=0.89
PFNA	0.09 (-0.12, 0.30) *P*=0.40	-0.49 (-1.36, 0.27) *P*=0.27	-0.05 (-0.46, 0.37) *P*=0.83
	HbA1c (%)		
PFOS	-0.004 (-0.01, 0.005) *P*=0.32	0.003 (-0.04, 0.05) *P*=0.79	-0.009 (-0.03, 0.01) *P*=0.37
PFOA	-0.007 (-0.02, 0.004) *P*=0.24	-0.033 (-0.10, 0.04) *P*=0.35	0.0002 (-0.02, 0.02) *P*=0.98
PFHxS	-0.006 (-0.01, 0.001) *P*=0.13	0.013 (-0.03, 0.06) *P*=0.58	-0.006 (-0.02, 0.005) *P*=0.44
Et-PFOSA-AcOH	0.001 (-0.01, 0.01) *P*=0.78	-0.007 (-0.05, 0.03) *P*=0.70	-0.004 (-0.01, 0.001) *P*=0.45
Me-PFOSA-AcOH	0.007 (-0.001, 0.01) *P*=0.06	0.016 (-0.03, 0.06) *P*=0.50	-0.007 (-0.02, 0.007) *P*=0.32
PFNA	0.001 (-0.006, 0.01) *P*=0.88	0.006 (-0.04, 0.05) *P*=0.79	-0.009 (-0.02, 0.006) *P*=0.23
	Fasting Pro-insulin (pM)		
PFOS	-0.08 (-0.43, 0.26) *P*=0.63	1.16 (-0.32, 2.63) *P*=0.12	0.07 (-0.62, 0.75) *P*=0.85
PFOA	-0.01 (-0.40, 0.38) *P*=0.96	0.35 (-1.33, 2.02) *P*=0.68	-0.09 (-0.86, 0.69) *P*=0.82
PFHxS	-0.09 (-0.35, 0.15) *P*=0.44	0.34 (-0.82, 1.49) *P*=0.57	-0.26 (-0.77, 0.25) *P*=0.32
Et-PFOSA-AcOH	0.03 (-0.19, 0.25) *P*=0.91	0.35 (-0.59, 1.28) *P*=0.47	-0.26 (-0.77, 0.25) *P*=0.32
Me-PFOSA-AcOH	0.15 (-0.10, 0.40) *P*=0.25	-0.81 (-1.91, 0.28) *P*=0.14	0.13 (-0.31, 0.56) *P*=0.57
PFNA	0.06 (-0.19, 0.32) *P*=0.64	0.25 (-0.90, 1.40) *P*=0.67	-0.18 (-0.70, 0.33) *P*=0.49

Table S3 continued.

PFAS Analyte	Corrected Insulin Response		
	Model 1	Model 2	Model 3
log_2-PFAS	**$\beta(PFAS * time)$ Est. (95% CI)**	**$\beta(PFAS * Tx)$ Est. (95% CI)**	**$\beta(PFAS * time * Tx)$ Est. (95% CI)**
PFOS	-0.006 (-0.02, 0.004) *P*=0.28	0.02 (-0.03, 0.06) *P*=0.43	0.001 (-0.02, 0.02) *P*=0.91
PFOA	-0.011 (-0.02, 0.0004) *P*=0.06	-0.01 (-0.07, 0.04) *P*=0.62	-0.003 (-0.02, 0.02) *P*=0.78
PFHxS	-0.005 (-0.01, 0.003) *P*=0.20	-0.01 (-0.05, 0.02) *P*=0.44	0.006 (-0.01, 0.02) *P*=0.48
Et-PFOSA-AcOH	-0.004 (-0.01, 0.003) *P*=0.26	0.002 (-0.03, 0.03) *P*=0.91	0.002 (-0.01, 0.01) *P*=0.97
Me-PFOSA-AcOH	-0.002 (-0.01, 0.005) *P*=0.60	0.002 (-0.03, 0.03) *P*=0.91	0.002 (-0.01, 0.02) *P*=0.85
PFNA	-0.003 (-0.01, 0.004) *P*=0.43	-0.02 (-0.02, 0.06) *P*=0.26	-0.001 (-0.02, 0.02) *P*=0.90
	Insulinogenic index		
PFOS	0.003 (-0.07, 0.08) *P*=0.97	0.02 (-0.13, 0.16) *P*=0.84	*NA*
PFOA	0.02 (-0.06, 0.10) *P*=0.67	-0.02 (-0.18, 0.15) *P*=0.86	*NA*
PFHxS	0.02 (-0.04, 0.07) *P*=0.51	-0.08 (-0.19, 0.04) *P*=0.18	*NA*
Et-PFOSA-AcOH	-0.001 (-0.04, 0.05) *P*=0.97	-0.01 (-0.11, 0.08) *P*=0.79	*NA*
Me-PFOSA-AcOH	0.01 (-0.05, 0.06) *P*=0.84	0.01 (-0.10, 0.12) *P*=0.91	*NA*
PFNA	0.03 (-0.02, 0.09) *P*=0.27	0.13 (-0.20, 0.03) *P*=0.13	*NA*
	Adiponectin: Baseline-Year1 (Linear model for the difference)		
	$\beta(PFAS)$ Est. (95% CI)	**$\beta(PFAS * Tx)$† Est. (95% CI)**	
PFOS	-0.07 (-0.17, 0. 05) *P*=0.25	-0.10 (-0.32, 0.11) *P*=0.35	*NA*
PFOA	-0.08 (-0.17, 0.04) *P*=0.21	-0.06 (-0.31, 0.18) *P*=0.62	*NA*
PFHxS	-0.02 (-0.11, 0.07) *P*=0.60	-0.11 (-0.28, 0.06) *P*=0.20	*NA*
Et-PFOSA-AcOH	-0.04 (-0.11, 0.03) *P*=0.31	-0.07 (-0.21, 0.07) *P*=0.33	*NA*
Me-PFOSA-AcOH	-0.03 (-0.12, 0.05) *P*=0.43	**-0.17 (-0.21, 0.07)** *P*=0.05	*NA*
PFNA	-0.01 (-0.11, 0.08) *P*=0.75	-0.08 (-0.25, 0.09) *P*=0.33	*NA*

NA= Interaction between time and treatment was not necessary in these models (marginal for IGRAT $P>0.10$ and not applicable for the difference in adiponectin from baseline to year 1)

†= Reference treatment arm is the intensive lifestyle intervention

Table S4. [a]Adjusted Hazards Ratios (HRs) for time to first fasting hyperglycemia during study period relative to log_2-PFAS plasma concentrations in the Diabetes Prevention Program trial

PFAS Analyte	Crude HR (unadjusted)		Adjusted HR	
	[‡]Fasting hyperglycemia		[‡]Fasting hyperglycemia	
PFAS (log_2-scale)	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
PFOS	0.90 (0.65, 1.25)	0.55	0.88 (0.63, 1.24)	0.47
n-PFOS	0.95 (0.70, 1.29)	0.73	0.92 (0.67, 1.28)	0.63
Sm-PFOS	0.86 (0.62, 1.17)	0.33	0.84 (0.60, 1.17)	0.31
Sm2-PFOS	0.91 (0.71, 1.18)	0.51	0.93 (0.72, 1.21)	0.60
PFOA	1.10 (0.76, 1.58)	0.62	1.12 (0.76, 1.64)	0.56
n-PFOA	1.02 (0.70, 1.49)	0.93	1.04 (0.70, 1.54)	0.86
Sb-PFOA	**1.28 (1.03, 1.59)**	**0.03**	**1.29 (1.03, 1.63)**	**0.03**
PFHxS	0.90 (0.70, 1.15)	0.41	0.96 (0.73, 1.26)	0.76
Et-PFOSA-AcOH	0.97 (0.79, 1.19)	0.79	0.96 (0.76, 1.20)	0.70
Me-PFOSA-AcOH	1.16 (0.90, 1.49)	0.25	1.12 (0.85, 1.48)	0.41
PFNA	1.04 (0.81, 1.34)	0.74	1.04 (0.79, 1.36)	0.80

[a]Adjusted for participant sex, race/ethnicity, BMI (continuous), age (categorical), marital status (categorical), education (categorical), smoking history (categorical) and treatment assignment (Placebo/lifestyle)

[‡]n=47 cases of first fasting hyperglycemia (elevated glucose but diabetes was not confirmed at a follow-up visit)

Table S5. [a]Adjusted Hazards Ratios (HRs) for the risk of developing diabetes during study period relative to log_2-PFAS plasma concentrations stratified by treatment assignment

PFAS Analyte	Placebo (n=476)		Lifestyle intervention (n=481)		[b] Interaction test for treatment
PFAS (log_2-scale)	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	***P***
PFOS	0.91 (0.76, 1.12)	0.39	0.77 (0.57, 1.04)	0.09	0.65
n-PFOS	0.91 (0.76, 1.10)	0.34	0.78 (0.59, 1.04)	0.09	0.76
Sm-PFOS	0.96 (0.79, 1.15)	0.65	0.84 (0.63, 1.11)	0.22	0.62
Sm2-PFOS	1.03 (0.90, 1.19)	0.68	0.92 (0.74, 1.14)	0.44	0.37
PFOA	1.04 (0.83, 1.30)	0.73	1.06 (0.76, 1.46)	0.74	0.84
n-PFOA	1.01 (0.80, 1.27)	0.96	1.03 (0.73, 1.44)	0.88	0.84
Sb-PFOA	1.10 (0.96, 1.24)	0.18	1.11 (0.93, 1.32)	0.26	0.77
PFHxS	0.98 (0.83, 1.15)	0.77	1.01 (0.81, 1.26)	0.91	0.99
Et-PFOSA-AcOH	0.98 (0.86, 1.12)	0.77	0.93 (0.78, 1.12)	0.45	0.94
Me-PFOSA-AcOH	0.89 (0.77, 1.03)	0.13	1.14 (0.91, 1.42)	0.25	**0.04**
PFNA	1.00 (0.84, 1.17)	0.97	0.92 (0.73, 1.15)	0.46	0.78

[a]Adjusted for participant sex, race/ethnicity, BMI (continuous), age (categorical), marital status (categorical), education (categorical) and smoking history (categorical)

[b]Statistical test for multiplicative interaction in non-stratified models (i.e. interaction between treatment assignment and PFAS compound)

Table S6. [a]Adjusted Hazards Ratios (HRs) for the risk of developing diabetes during study period relative to log_2-PFAS plasma concentrations stratified by sex

PFAS Analyte	Male (n=332)		Female (n=625)		[b] Interaction test for gender
PFAS (log_2-scale)	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	***P***
PFOS	0.79 (0.61, 0.02)	0.07	0.90 (0.73, 1.10)	0.29	0.40
n-PFOS	0.80 (0.63, 1.02)	0.08	0.89 (0.73, 1.08)	0.24	0.50
Sm-PFOS	0.78 (0.61, 1.01)	0.06	0.97 (0.80, 1.17)	0.73	0.14
Sm2-PFOS	0.99 (0.82, 1.19)	0.92	0.98 (0.84, 1.15)	0.83	0.82
PFOA	0.89 (0.64, 1.22)	0.46	1.11 (0.89, 1.39)	0.35	0.31
n-PFOA	0.84 (0.60, 1.18)	0.31	1.09 (0.86, 1.37)	0.50	0.27
Sb-PFOA	1.05 (0.87, 1.27)	0.59	1.12 (0.98, 1.27)	0.08	0.63
PFHxS	0.89 (0.71, 1.13)	0.34	1.01 (0.86, 1.19)	0.86	0.40
Et-PFOSA-AcOH	0.87 (0.74, 1.03)	0.12	1.04 (0.91, 1.18)	0.61	0.11
Me-PFOSA-AcOH	0.88 (0.71, 1.09)	0.25	0.98 (0.84, 1.13)	0.80	0.35
PFNA	0.95 (0.75, 1.21)	0.67	0.99 (0.84, 1.16)	0.90	0.92

[a]Adjusted for participant race/ethnicity, BMI (continuous), age (categorical), marital status (categorical), education (categorical), smoking history (categorical) and treatment assignment.

[b]Statistical test for multiplicative interaction in non-stratified models (i.e. interaction between sex and PFAS compound) adjusted for covariates

Table S7. [a]Adjusted Hazards Ratios (HRs) for the risk of developing diabetes during study period: multiplicative interaction between baseline log_2-PFAS plasma concentrations and BMI at baseline.

BMI *x* PFAS (log_2-scale)	Hazard Ratio (HR)	
	HR (95% CI)	***P***
PFOS	0.99 (0.97, 1.02)	0.66
n-PFOS	0.99 (0.98, 1.01)	0.84
Sm-PFOS	0.99 (0.97, 1.01)	0.37
Sm2-PFOS	0.99 (0.98, 1.01)	0.90
PFOA	0.99 (0.97, 1.02)	0.57
n-PFOA	0.99 (0.96, 1.02)	0.43
Sb-PFOA	1.00 (0.99, 1.02)	0.66
PFHxS	1.00 (0.98, 1.01)	0.77
Et-PFOSA-AcOH	0.99 (0.97, 1.01)	0.51
Me-PFOSA-AcOH	1.00 (0.98, 1.01)	0.66
PFNA	0.99 (0.98, 1.01)	0.54

[a]Adjusted for participant sex, race/ethnicity, BMI (continuous), age (categorical), marital status (categorical), education (categorical), smoking history (categorical) and treatment assignment.

[b]Statistical test for multiplicative interaction in adjusted models (i.e. interaction between baseline BMI and PFAS plasma concentrations)

Appendix A. Longitudinal Regression Model Equations

In **Model 1** we generate an effect estimate for each PFAS over the follow-up time. The model equation is

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 \text{PFAS}_i + \beta_4 \text{Tx}_i +$$
$$\beta_5 t_{ij} * \text{Tx}_i + \beta_6 \text{PFAS}_i * t_{ij} + \cdots + b_{0i} + b_{1i} t_{ij} + e_{ij}$$

where i indexes the study participants and j the study visit number, y_{ij} is the glycemic outcome for person i at visit number j, t_{ij} is the time since randomization at visit ij, PFAS_i is the baseline PFAS measurement for subject i, and Tx_i indicates treatment arm assignment (1 for lifestyle, 0 for placebo). The ellipsis indicates adjustment covariates. The model definition is completed by the assumption that e_{ij} is distributed normal and indepdent from (b_{0i}, b_{1i}), which is assumed multivariate normal.

In addition, if a significant quadratic interaction between time and the intervention was observed, then the following model was used instead:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 \text{PFAS}_i + \beta_4 \text{Tx}_i +$$
$$\beta_5 t_{ij} * \text{Tx}_i + \beta_6 t_{ij}^2 * \text{Tx}_i + \beta_7 \text{PFAS}_i * t_{ij} + \cdots + b_{0i} + b_{1i} t_{ij} + e_{ij}$$

where the notation and assumptions from equation 1 are unchanged.

In **Model 2**, we generate an effect estimate for each PFAS by treatment assignment, by introducing an interaction between the baseline PFAS and the treatment group indicator:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 \text{PFAS}_i + \beta_4 \text{Tx}_i +$$
$$\beta_5 t_{ij} * \text{Tx}_i + \beta_6 t_{ij}^2 * \text{Tx}_i + \beta_7 \text{PFAS}_i * t_{ij} + \beta_8 \text{PFAS}_i * \text{Tx}_i + \cdots + b_{0i} + b_{1i} t_{ij} + e_{ij}$$

where the notation and assumptions from equation 1 are unchanged.

In **Model 3**, we allow each PFAS to have a different effect over time in each treatment group, with a three-way interaction among PFAS, treatment group, and time:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 \text{PFAS}_i + \beta_4 \text{Tx}_i +$$
$$\beta_5 t_{ij} * \text{Tx}_i + \beta_6 t_{ij}^2 * \text{Tx}_i + \beta_7 \text{PFAS}_i * t_{ij} + \beta_8 \text{PFAS}_i * \text{Tx}_i + \beta_9 \text{PFAS}_i * \text{Tx}_i * t_{ij} +$$
$$\ldots + b_{0i} + b_{1i} t_{ij} + e_{ij}$$