SUPPLEMENTARY DATA

*eTable S1. Geometric means (GMs) and inter-quartile range (IQR) of plasma perfluoroalkyl and polyfluoroalkyl substances (PFASs) concentration measured at baseline and 2-years post-randomization and spearman correlations (r_s) between baseline and year-2 concentrations in the Diabetes Prevention Program (DPP); N=957.

PFAS biomarkers	Chemical Name	Baseline		Year-2		Spearman correlation
		<LOD n (%)	GM (IQR) ng/mL	<LOD n (%)	GM (IQR) ng/mL	r_s
Sum PFAS	Sum PFASs	0	38.43 (28.60)	0	41.12 (27.1)	0.92
PFOS	Perfluorooctane sulfonic acid	0	26.38 (22.80)	0	28.13 (19.2)	0.69
n-PFOS	Linear perfluorooctane sulfonic acid	0	18.42 (16.9)	0	20.39 (14.6)	0.67
Sm-PFOS	Perfluoromethylheptane sulfonic acids	0	7.32 (6.50)	0	7.35 (5.6)	0.60
Sm2-PFOS	Perfluorodimethylhexane sulfonic acids	564 (58.9%)	0.13 (0.23)	557 (58.2%)	0.13 (0.23)	0.33
PFOA	Perfluorooctanoic acid	0	4.82 (3.20)	0	5.77 (4.0)	0.68
n-PFOA	Linear perfluorooctanoic acid	0	4.29 (2.90)	0	4.85 (3.0)	0.74
Sb-PFOA	Branched perfluorooctanoic acids	159 (16.6%)	0.44 (0.50)	101 (10.6%)	0.61 (0.8)	0.49
PFHxS	Perfluorohexane sulfonic acid	1 (0.1%)	2.41 (2.40)	9 (0.9%)	2.42 (2.4)	0.82
EtFOSAA	*N*-ethyl-perfluorooctane sulfonamido acetic acid	32 (3.3%)	1.13 (1.50)	76 (7.9%)	0.94 (1.3)	0.48
MeFOSAA	*N*-methyl-perfluorooctane sulfonamido acetic acid	29 (2.6%)	0.94 (1.10)	32 (3.3%)	1.03 (1.0)	0.41
PFNA	Perfluorononanoic acid	65 (6.8%)	0.53 (0.40)	46 (4.8%)	0.58 (0.5)	0.78

LOD = Limit of Detection; LOD was 0.1 ng/mL for all analytes

IQR = Inter-Quartile Range

PFOS = n-PFOS + Sm-PFOS + Sm2-PFOS

PFOA = n-PFOA + Sb-PFOA

*Partial data from this table has been previously published in: Cardenas, Andres, *et al*. "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." *Environmental health perspectives* 125.10 (2017): 107001.

SUPPLEMENTARY DATA

eTable S2. [a] Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) for diabetes incidence during follow-up relative to baseline plasma PFAS concentration categorized in tertiles overall and stratified by baseline treatment.

PFAS	**Overall** N=956 (507 cases)		**Placebo** N=476 (272 cases)		**Lifestyle** N=480 (235 cases)	
	HR (95% CI)	*P*	**HR (95% CI)**	*P*	**HR (95% CI)**	*P*
Sum PFAS						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	0.97 (0.77, 1.22)	0.59	0.94 (0.69, 1.30)	0.74	1.00 (0.71, 1.41)	0.93
Tertile 3	0.94 (0.75, 1.18)		0.95 (0.69, 1.30)		0.99 (0.70, 1.39)	
PFOS						
Tertile 1	*Ref*		*Ref*		*Ref*	0.54
Tertile 2	0.96 (0.77, 1.20)	0.30	0.83 (0.61, 1.13)	0.47	1.17 (0.83, 1.64)	
Tertile 3	0.89 (0.71, 1.11)		0.90 (0.66, 1.22)		0.92 (0.64, 1.29)	
n-PFOS						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	1.00 (0.80, 1.26)	0.27	0.85 (0.63, 1.16)	0.69	1.25 (0.89, 1.78)	0.60
Tertile 3	1.09 (0.73, 1.15)		0.94 (0.69, 1.29)		0.94 (0.66, 1.33)	
Sm-PFOS						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	0.94 (0.75, 1.18)	0.27	1.04 (0.76, 1.42)	0.75	0.88 (0.63, 1.22)	0.26
Tertile 3	0.88 (0.71, 1.10)		0.95 (0.70, 1.29)		0.83 (.0.59, 1.15)	
Sm2-PFOS						
<Median	*Ref*	0.85	*Ref*	0.37	*Ref*	0.36
≥Median	1.02 (0.85, 1.22)		1.12 (0.87, 1.45)		0.88 (0.67, 1.16)	
PFOA						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	0.94 (0.75, 1.17)	0.62	0.93 (0.68, 1.27)	0.72	0.88 (0.63, 1.23)	0.37
Tertile 3	0.94 (0.75, 1.18)		1.06 (0.77, 1.47)		0.86 (0.61, 1.20)	
Sb-PFOA						
Tertile 1	*Ref*		**Ref**		*Ref*	
Tertile 2	1.12 (0.90, 1.40)	0.13	**1.53 (1.12, 2.10)**	**0.002**	0.69 (0.49, 1.10)	0.36
Tertile 3	1.18 (0.95, 1.46)		**1.61 (1.18, 2.19)**		0.88 (0.64, 1.21)	
PFHxS						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	0.80 (0.64, 1.02)	0.07	0.78 (0.58, 1.06)	0.07	0.69 (0.47, 1.00)	0.91
Tertile 3	0.81 (0.64, 1.01)		0.75 (0.54, 1.04)		0.95 (0.66, 1.35)	
EtFOSAA						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	1.03 (0.83, 1.29)	0.84	0.96 (0.70, 1.32)	0.93	1.13 (0.79, 1.60)	0.67
Tertile 3	1.02 (0.82, 1.28)		0.99 (0.72, 1.35)		1.08 (0.77, 1.55)	
MeFOSAA						
Tertile 1	*Ref*		*Ref*		*Ref*	
Tertile 2	1.03 (0.82, 1.29)	0.65	1.06 (0.77, 1.45)	0.91	0.96 (0.69, 1.34)	0.61
Tertile 3	0.95 (0.75, 1.19)		0.98 (0.71, 1.36)		0.91 (0.65, 1.29)	
PFNA						

Tertile 1		*Ref*				*Ref*			*Ref*	
Tertile 2		0.96 (0.77, 1.21)	0.68			1.07 (0.78, 1.48)	0.48		0.86 (0.61, 1.20)	0.98
Tertile 3		1.06 (0.83, 1.34)				1.13 (0.81, 1.56)			1.02 (0.70, 1.47)	

[a] Adjusted for participant sex, race/ethnicity, and baseline age, marital status, education, income, smoking history, BMI, maternal diabetes, paternal diabetes and treatment assignment if not stratified.

eTable S3. [a] Adjusted Odds Ratios (ORs) and 95% confidence intervals (95% CIs) for specific microvascular disease prevalence at the end of DPOS by baseline plasma PFAS concentration

PFAS (log$_2$-scale)	Nephropathy N=871 (n=110 cases) OR (95% CI)	Neuropathy N=713 (n=88 cases) OR (95% CI)	Retinopathy N=801 (n=98 cases) OR (95% CI)
Sum PFAS	1.13 (0.87, 1.46)	1.10 (0.79, 1.54)	1.12 (0.85, 1.46)
PFOS	1.12 (0.89, 1.41)	1.03 (0.77, 1.40)	1.10 (0.86, 1.41)
n-PFOS	1.12 (0.90, 1.41)	0.99 (0.74, 1.32)	1.11 (0.87, 1.41)
Sm-PFOS	1.06 (0.85, 1.33)	1.13 (0.85, 1.50)	1.09 (0.87, 1.37)
Sm2-PFOS	1.13 (0.95, 1.34)	1.20 (0.97, 1.48)	**1.23 (1.03, 1.47)**
PFOA	0.91 (0.69, 1.20)	1.04 (0.75, 1.46)	1.08 (0.82, 1.41)
n-PFOA	0.91 (0.68, 1.21)	1.05 (0.74, 1.48)	1.05 (0.79, 1.39)
Sb-PFOA	0.99 (0.86, 1.15)	1.03 (0.87, 1.24)	1.13 (0.97, 1.32)
PFHxS	0.98 (0.80, 1.20)	1.19 (0.93, 1.51)	1.09 (0.89, 1.33)
EtFOSAA	1.12 (0.97, 1.29)	1.08 (0.90, 1.30)	1.07 (0.91, 1.26)
MeFOSAA	1.06 (0.88, 1.29)	1.20 (0.94, 1.53)	0.90 (0.74, 1.10)
PFNA	1.00 (0.82, 1.22)	1.16 (0.91, 1.50)	1.14 (0.93, 1.42)

[a] Adjusted for participant sex, race/ethnicity, and baseline age, marital status, education, income, smoking history, BMI, maternal diabetes, paternal diabetes and treatment assignment if not stratified.

SUPPLEMENTARY DATA

eTable S4. Mean change of plasma perfluoroalkyl and polyfluoroalkyl substances (PFAS) concentrations from baseline to 2-years post-randomization stratified by treatment.

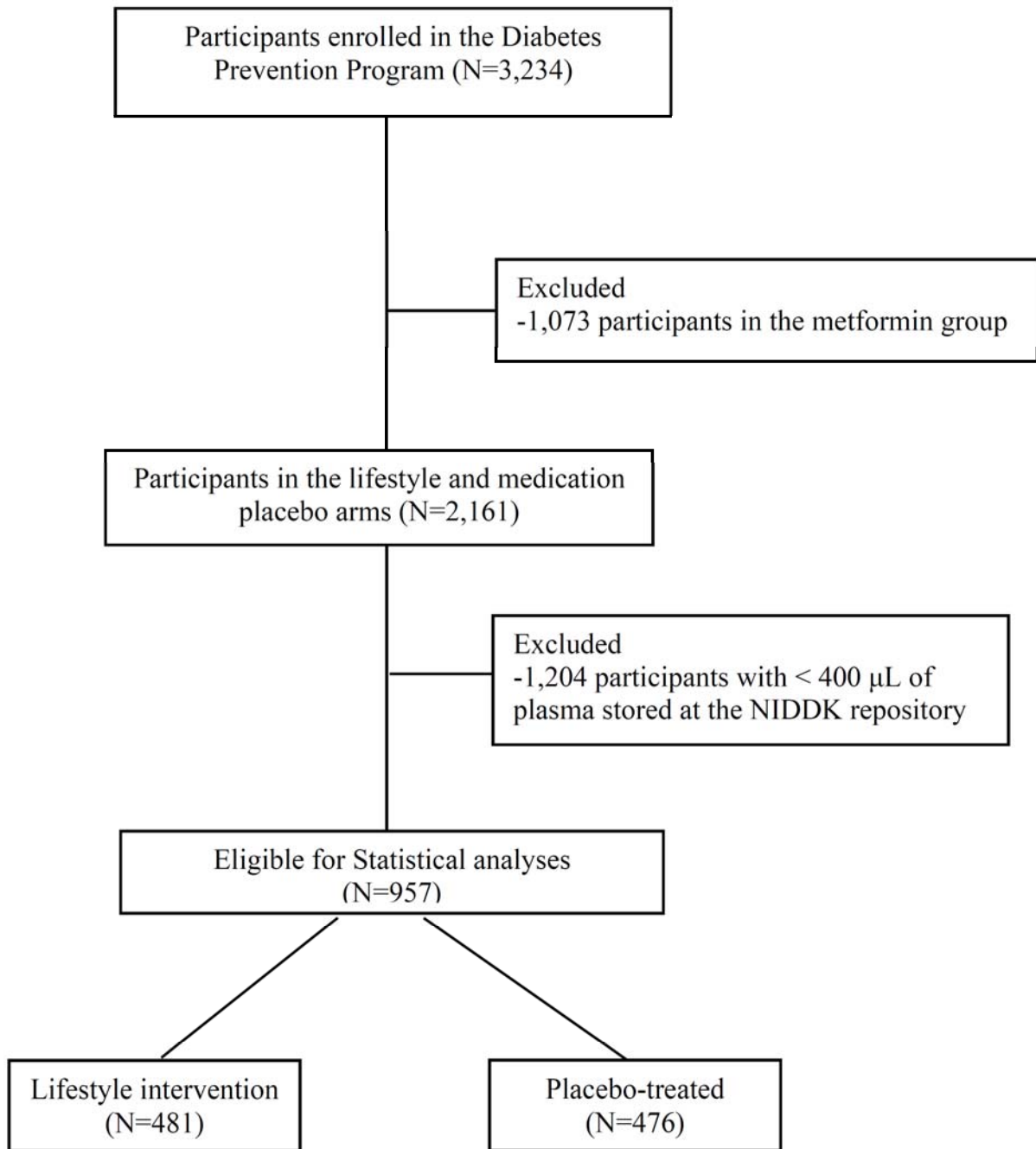| PFASs	Placebo	Lifestyle	
	Mean change (95% CI) (ng/mL)	Mean change (95% CI) (ng/mL)	*p*
Sum PFAS	-0.95 (-1.86, -0.05)	-1.14 (-2.11, -0.18)	0.78
PFOS	0.49 (-0.98, 1.97)	1.38 (-0.13, 2.89)	0.41
n-PFOS	0.91 (-0.22, 2.05)	1.71 (0.55, 2.88)	0.33
Sm-PFOS	-0.38 (-0.86, 0.10)	-0.32 (-0.83, 0.19)	0.87
Sm2-PFOS	---	---	---
PFOA	1.54 (1.21, 1.86)	0.92 (0.57, 1.26)	0.0011
n-PFOA	0.57 (0.37, 0.76)	0.60 (0.35, 0.86)	0.82
Sb-PFOA	0.96 (0.71, 1.22)	0.31 (0.14, 0.48)	3.56×10^{-5}
PFHxS	-0.06 (-0.22, 0.11)	-0.13 (-0.32, 0.07)	0.61
EtFOSAA	-0.28 (-0.49, -0.08)	-0.08 (-0.34, 0.19)	0.24
MeFOSAA	0.16 (0.02, 0.31)	0.13 (-0.07, 0.34)	0.83
PFNA	0.06 (0.02, 0.09)	0.07 (0.03, 0.10)	0.72

SUPPLEMENTARY DATA

eTable S5. Geometric means (GMs), inter-quartile ranges (IQR) and proportion of samples below the limit of detection (LOD) for plasma Sb-PFOA concentration by treatment assignment at baseline and 2-years post-randomization.

| Sb-PFOA	Baseline			2-years post-randomization		
	Placebo	Lifestyle	*p*	Placebo	Lifestyle	*p*
GM (IQR) ng/mL	0.44 (0.50)	0.44 (0.60)	0.93	0.73 (0.80)	0.52 (0.70)	1.65×10^{-5}
% below LOD	15.76%	17.46%	0.53	8.19%	12.89%	0.02

SUPPLEMENTARY DATA

eFigure S1. Participant flow diagram selected for analyses of plasma PFAS concentration from the Diabetes Prevention Program Trial

Participants enrolled in the Diabetes
Prevention Program (N=3,234)

Excluded
-1,073 participants in the metformin group

Participants in the lifestyle and medication
placebo arms (N=2,161)

Excluded
-1,204 participants with < 400 μL of
plasma stored at the NIDDK repository

Eligible for Statistical analyses
(N=957)

Lifestyle intervention
(N=481)

Placebo-treated
(N=476)

SUPPLEMENTARY DATA

eFigure S2. Cumulative incidence of diabetes, excluding participants that developed diabetes (N=204) during DPP, for participants with plasma Sb-PFOA at or below median concentration (≤0.5 ng/mL) and among participants with above median Sb-PFOA concentration for **A)** placebo treated group and **B)** lifestyle intervention group.
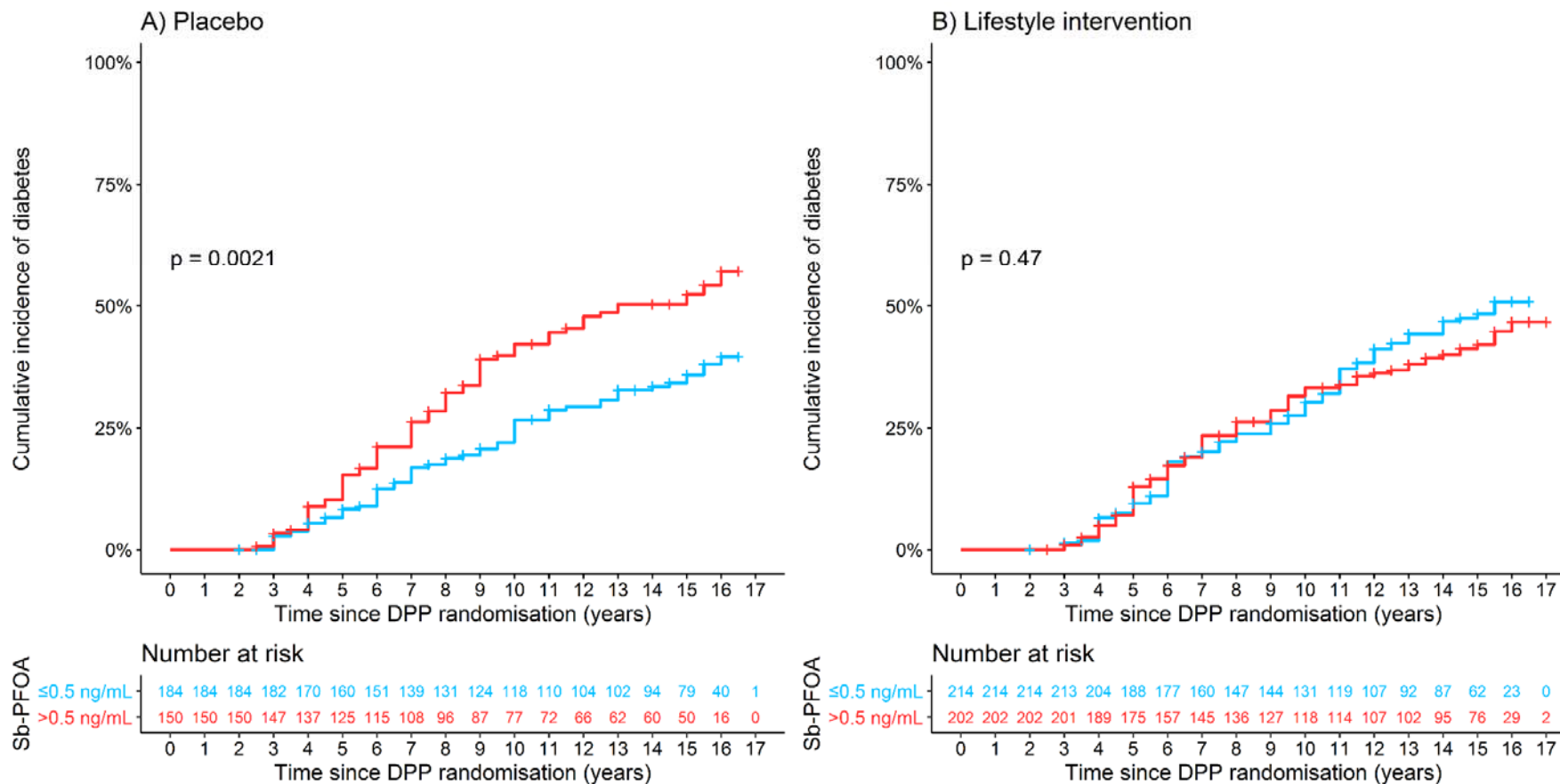
eFigure S3. [a] Adjusted estimated change in hemoglobin A_{1c} (HbA_{1c}) from baseline, stratified by treatment, for the 25th and 75th percentiles of plasma Sb-PFOA concentration.
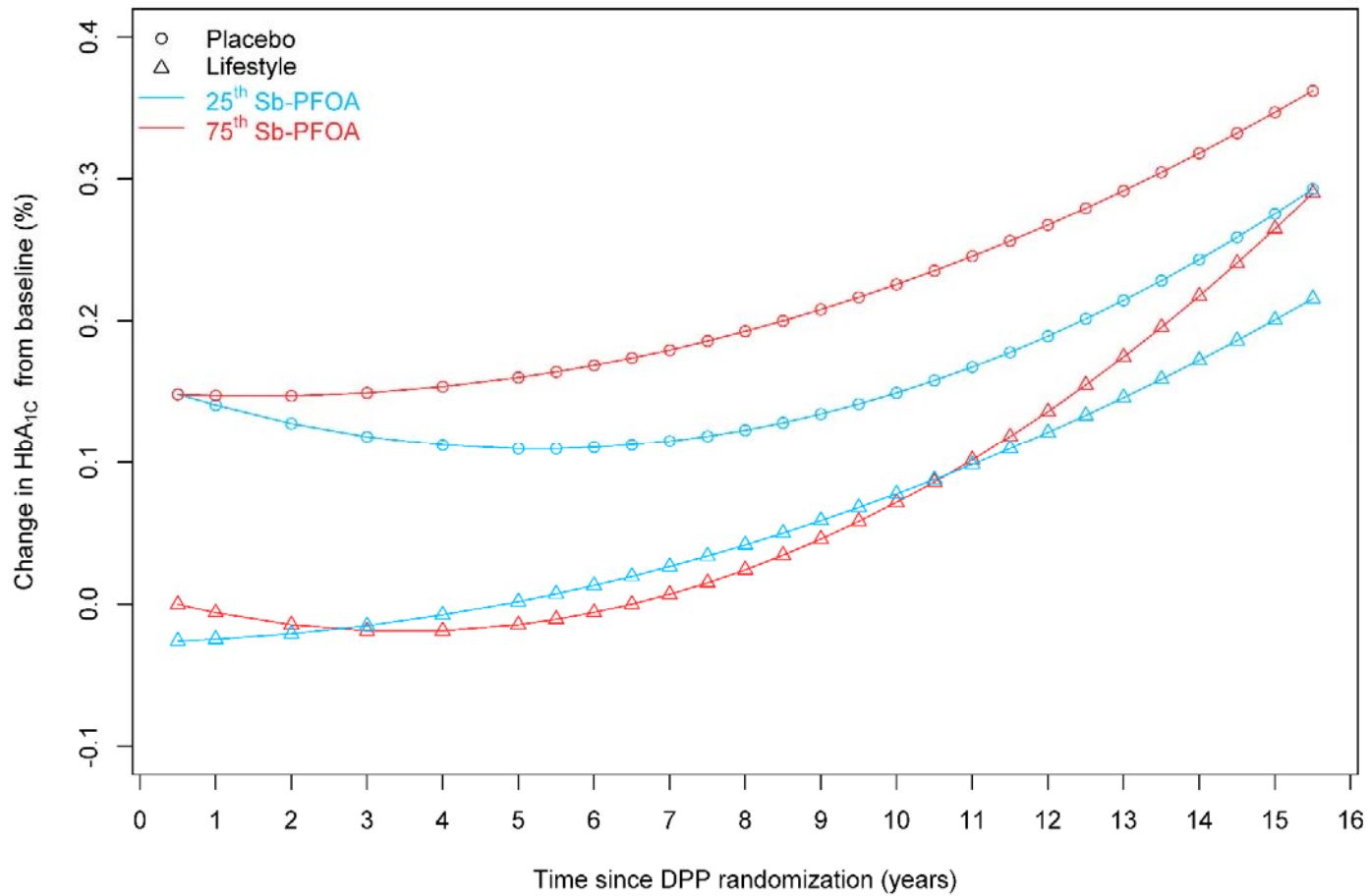
[a] Adjusted for participant sex, race/ethnicity, and baseline age, marital status, education, income, smoking history, BMI, maternal diabetes and paternal diabetes