SUPPLEMENTARY DATA

Supplementary Table 1a. Comparison of baseline characteristics of participants excluded and included in cognitive assessments in the Lifestyle group of the Diabetes Prevention Program Outcomes Study. Characteristics are from the time of randomization in the Diabetes Prevention Program. P-values are from Pearson's Chi-square test for categorical variables and ANOVA test for continuous variables.

Characteristic	**Excluded (n=330)**	**Included (n=749)**	**p-value**
Age at randomization (years)	49.0 ± 12.5	51.3 ± 10.7	0.002
Women (%)	228 (69.1)	506 (67.6)	0.62
Education			0.22
≤ 12 yrs (%)	97 (29.4)	183 (24.4)	
13-16 yrs (%)	150 (45.4)	372 (49.7)	
≥ 17 yrs (%)	83 (25.2)	194 (25.9)	
Race/Ethnicity			0.02
White (%)	178 (54.0)	402 (53.7)	
African American (%)	54 (16.4)	150 (20.0)	
Hispanic (%)	71 (21.5)	107 (14.3)	
American Indian (%)	14 (4.2)	46 (6.1)	
Asian (%)	13 (3.9)	44 (5.9)	
APOE-ε4			0.22
Positive	60 (21.7)	159 (25.4)	
Negative	217 (78.3)	466 (74.6)	
Fasting Glucose (mg/dl)	106.4 ± 8.2	106.2 ± 8.0	0.82
Hemoglobin A1C			0.91
%	5.91 ± 0.52	5.91 ± 0.49	
mmol/mol	41 ± 5.7	41 ± 5.4	
Cholesterol (mg/dl)	202.3 ± 38.4	204.6 ± 35.9	0.33
Triglycerides (mg/dl)	165.3 ± 105.9	161.6 ± 93.4	0.57
HDL (mg/dl)	45.4 ± 12.2	46.3 ± 12.5	0.25
SF-36* Mental	53.5 ± 8.5	53.9 ± 7.1	0.37
SF-36* Physical	50.4 ± 7.3	50.7 ± 6.7	0.47
SBP † (mmHg)	124.5 ± 15.0	123.3 ± 14.7	0.24
DBP ‡ (mmHg)	79.4 ± 8.7	78.3 ± 9.3	0.06
Beck Depression Inventory (BDI)	4.81 ± 4.87	4.43 ± 4.39	0.21
Leisure Activity (Met-hours)	14.9 ± 22.6	15.8 ± 21.9	0.58

* Short form health survey
† Systolic blood pressure
‡ Diastolic blood pressure

SUPPLEMENTARY DATA

Supplementary Table 1b. Comparison of baseline characteristics of participants excluded and included in cognitive assessments in the metformin group. Characteristics are from the time of randomization in the Diabetes Prevention Program. P-values are from Pearson's Chi-square test for categorical variables and ANOVA test for continuous variables.

Characteristic	**Excluded (n=297)**	**Included (n=776)**	**p-value**
Age at randomization (years)	49.2 ± 11.8	51.5 ± 9.6	0.001
Women (%)	197 (66.3)	513 (66.1)	0.95
Education			0.07
≤ 12 years (%)	84 (28.3)	185 (23.8)	
13-16 years (%)	147 (49.5)	367 (47.3)	
≥ 17 years (%)	66 (22.2)	224 (28.9)	
Race/Ethnicity			0.92
White (%)	169 (56.9)	433 (55.8)	
African American (%)	58 (19.5)	163 (21.0)	
Hispanic (%)	48 (16.2)	114 (14.7)	
American Indian (%)	13 (4.4)	39 (5.0)	
Asian (%)	9 (3.0)	27 (3.5)	
APOE-ε4			0.14
Positive	79 (31.7)	171 (26.7)	
Negative	170 (68.3)	469 (73.3)	
Fasting Glucose (mg/dl)	106.4 ± 8.1	106.6 ± 8.6	0.84
Hemoglobin A1C			0.33
%	5.89 ± 0.51	5.92 ± 0.50	
mmol/mol	41 ± 5.6	41 ± 5.5	
Cholesterol (mg/dl)	200.5 ± 38.6	203.5 ± 34.4	0.21
Triglycerides (mg/dl)	156.1 ± 92.8	159.6 ± 89.1	0.57
HDL (mg/dl)	45.4 ± 11.1	46.3 ± 11.6	0.21
SF-36* Mental	53.8 ± 7.9	54.2 ± 7.6	0.55
SF-36* Physical	49.9 ± 7.5	50.1 ± 7.2	0.68
SBP † (mmHg)	124.2 ± 14.5	124.0 ± 15.1	0.84
DBP ‡ (mmHg)	78.5 ± 9.4	78.1 ± 9.6	0.57
Beck Depression Inventory (BDI)	5.02 ± 4.68	4.34 ± 4.28	0.02
Leisure Activity (Met-hours)	15.1 ± 34.5	16.9 ± 21.7	0.30

* Short form health survey
† Systolic blood pressure
‡ Diastolic blood pressure

SUPPLEMENTARY DATA

Supplementary Table 1c. Comparison of baseline characteristics of participants excluded and included in cognitive assessments in the Placebo group. Characteristics are from the time of randomization in the Diabetes Prevention Program. P-values are from Pearson's Chi-square test for categorical variables and ANOVA test for continuous variables.

Characteristic	**Excluded (n=327)**	**Included (n=755)**	**p-value**
Age at randomization (years)	49.8 ± 12.3	50.5 ± 9.5	0.30
Women (%)	223 (68.2)	524(69.4)	0.69
Education			0.54
≤ 12 years (%)	89 (27.2)	196 (26.0)	
13-16 years (%)	149 (45.6)	371 (49.1)	
≥ 17 years (%)	89 (27.2)	188 (24.9)	
Race/Ethnicity			0.87
White (%)	176 (53.8)	410 (54.4)	
African American (%)	62 (19.0)	158 (20.9)	
Hispanic (%)	56 (17.1)	112 (14.8)	
American Indian (%)	18 (5.5)	41 (5.4)	
Asian (%)	15 (4.6)	34 (4.5)	
APOE-ε4			0.95
Positive	73 (27.6)	176 (27.5)	
Negative	191 (72.4)	465 (72.5)	
Fasting Glucose (mg/dl)	106.8 ± 7.9	106.7 ± 8.6	0.84
Hemoglobin A1C			0.07
%	5.87 ± 0.50	5.93 ± 0.51	
mmol/mol	41 ± 5.5	41 ± 5.6	
Cholesterol (mg/dl)	201.7 ± 39.2	203.1 ± 35.6	0.56
Triglycerides (mg/dl)	166.6 ± 89.8	169.6 ± 103.7	0.65
HDL (mg/dl)	44.0 ± 10.5	45.1 ± 11.8	0.14
SF-36* Mental	53.7 ± 8.5	54.2 ± 6.8	0.33
SF-36* Physical	49.9 ± 7.3	50.5 ± 7.1	0.19
SBP † (mmHg)	124.8 ± 14.4	122.9 ± 14.4	0.04
DBP ‡ (mmHg)	78.0 ± 8.9	78.0 ± 9.3	0.97
Beck Depression Inventory (BDI)	4.99 ± 5.33	4.44 ± 4.44	0.08
Leisure Activity (Met-hours)	15.9 ± 18.1	17.5 ± 32.7	0.41

* Short form health survey
† Systolic blood pressure
‡ Diastolic blood pressure

SUPPLEMENTARY DATA

Supplementary table 2. Comparison of cognitive function in Year 8 of the Diabetes Prevention Program Outcomes Study by treatment group and by age group at randomization. Data are presented as mean ± standard deviation. P-values are from the ANOVA test. The tests compared are the Spanish English Verbal Learning Test (SEVLT), the Digit Symbol Substitution Test (DSST), animal fluency, letter fluency, and a composite Z score. The distribution of participants by age group and treatment group is as follows: for lifestyle, 218 participants with age < 45 years, 361 participants with age 45 to 59 years, and 170 participants with age ≥ 60 years; for metformin, 201 participants with age < 45 years, 414 participants with age 45 to 59 years, and 161 participants with age ≥ 60 years; for placebo, 201 participants with age < 45 years, 425 participants with age 45 to 59 years, and 129 participants with age ≥ 60 years.

Age group	Lifestyle (n=749)	Metformin (n=776)	Placebo (n=755)	p-value
Total correct for SEVLT				0.61
Age < 45 years (n = 620)	39.97 ± 7.27	39.95 ± 8.42	39.53 ± 7.73	
Age 45 to 59 years (n = 1200)	37.26 ± 8.03	36.81 ± 8.53	36.59 ± 8.09	
Age ≥ 60 years (n = 460)	30.04 ± 9.25	30.03 ± 9.41	31.02 ± 9.78	
Total correct on DSST				0.51
Age < 45 years (n = 620)	55.91 ± 10.95	57.34 ± 11.99	56.71 ± 11.09	
Age 45 to 59 years (n = 1200)	49.41 ± 11.25	48.55 ± 11.29	49.20 ± 11.28	
Age ≥ 60 years (n = 460)	38.63 ± 9.97	39.54 ± 10.57	41.04 ± 11.21	
Total correct for animal fluency				0.32
Age < 45 years (n = 620)	21.38 ± 5.09	21.38 ± 4.82	21.08 ± 4.85	
Age 45 to 59 years (n = 1200)	19.85 ± 4.95	20.07 ± 4.88	19.54 ± 5.07	
Age ≥ 60 years (n = 460)	16.75 ± 4.93	16.09 ± 5.42	16.85 ± 5.42	
Total correct for letter fluency				0.52
Age < 45 years (n = 620)	14.05 ± 4.49	13.63 ± 4.36	13.70 ± 4.32	
Age 45 to 59 years (n = 1200)	13.20 ± 4.47	13.30 ± 4.50	13.16 ± 4.50	
Age ≥ 60 years (n = 460)	12.23 ± 4.78	11.51 ± 4.37	12.28 ± 5.21	
Composite z-score				0.5063
Age < 45 years (n = 620)	0.366 ± 0.668	0.370 ± 0.664	0.336 ± 0.629	
Age 45 to 59 years (n = 1200)	0.040 ± 0.700	0.030 ± 0.686	0.001 ± 0.687	
Age ≥ 60 years (n = 460)	-0.577 ± 0.744	-0.626 ± 0.722	-0.490 ± 0.817	

SUPPLEMENTARY DATA

Supplementary Table 3. Comparison of performance in cognitive tests between men and women in year 8 of the Diabetes Prevention Program Outcomes Study.

Test	Men (n=737)	Women (n=1543)	p value
Spanish English Verbal Learning Test	31.6 ± 8.9	38.6 ± 8.1	<0.001
Digit Symbol Substitution Test	44.7 ± 11.5	51.4 ± 12.5	<0.001
Animal fluency	18.7 ± 5.3	20.0 ± 5.2	<0.001
Letter fluency	12.5 ± 4.5	13.5 ± 4.6	<0.001

SUPPLEMENTARY DATA

Supplementary Table 4. Comparison of performance in cognitive tests between APOE-ε4 negative and positive participants in year 8 of the Diabetes Prevention Program Outcomes Study.

Test	**APOE-ε4 negative (n = 1400)**	**APOE-ε4 positive (n= 506)**	**p value**
Spanish English Verbal Learning Test	36.5 ± 9.1	35.9 ± 9.0	0.18
Digit Symbol Substitution Test	49.4 ± 12.7	48.8 ± 12.3	0.38
Animal fluency	19.7 ± 5.3	19.4 ± 5.2	0.30
Letter fluency	13.0 ± 4.6	13.4 ± 4.5	0.09

SUPPLEMENTARY DATA

Supplementary Table 5. P values from Interaction terms comparing cognitive scores across age (< 45 years, 45 to 59 years, ≥ 60 years), sex (men, women), APOE-ε4 (positive, negative), and diabetes (yes, no) groups from analysis of covariance.

Cognitive Function Variables	Age Categories	Sex	APOE-ε4	Diabetes
Total correct for the English Spanish Verbal Learning Test	0.61	0.17	0.67	0.32
Total correct on the Digit Symbol Substitution Test	0.51	0.53	0.81	0.31
Total correct on word fluency	0.52	0.49	0.40	0.84
Total correct on animal fluency	0.32	0.71	0.60	0.60

SUPPLEMENTARY DATA

Supplementary Table 6. Association between HbA1c at Year 8 and cognitive performance at Years 8 and 10 as well as the change between Year 8 and Year 10. Results are presented as regression coefficients (β) and p-values. Both unadjusted models and models adjusting for age, sex, education, and randomization arm are presented.

	Unadjusted Model		Adjusted Model	
	β	p value	β	p value
Total correct for SEVLT				
Year 8	0.057	0.791	-0.495	0.008
Year 10	0.013	0.946	-0.501	0.004
Difference	0.052	0.740	0.001	0.995
Total correct on DSST				
Year 8	0.326	0.276	-0.775	0.002
Year 10	0.295	0.286	-0.823	<.001
Difference	0.352	0.021	0.306	0.052
Total correct for animal fluency				
Year 8	0.009	0.940	-0.239	0.046
Year 10	-0.081	0.478	-0.355	0.001
Difference	0.025	0.812	-0.023	0.834
Total correct for letter fluency				
Year 8	-0.062	0.566	-0.142	0.183
Year 10	-0.097	0.328	-0.177	0.075
Difference	0.073	0.416	0.064	0.497
Composite z-score				
Year 8	0.004	0.807	-0.049	0.001
Year 10	-0.002	0.884	-0.057	<.001
Difference	0.013	0.186	0.008	0.439

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