Metformin, Lifestyle Intervention, and Cognition in the Diabetes Prevention Program Outcomes Study

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OBJECTIVE

We examined the association of the Diabetes Prevention Program (DPP) intervention arms (lifestyle intervention, metformin, and placebo) with cognition in the Diabetes Prevention Program Outcomes Study (DPPOS). We also examined metformin use, incident type 2 diabetes, and glycemia as exposures.

RESEARCH DESIGN AND METHODS

The DPP lasted 2.8 years, followed by a 13-month bridge to DPPOS. Cognition was assessed in DPPOS years 8 and 10 (12 and 14 years after randomization) with the Spanish English Verbal Learning Test (SEVLT), letter fluency and animal fluency tests, Digit Symbol Substitution Test (DSST), and a composite cognitive score.

RESULTS

A total of 2,280 participants (749 lifestyle, 776 metformin, and 755 placebo) aged 63.1 ± 10.7 years underwent cognitive assessments; 67.7% women, 54.6% non-Hispanic white, 20.7% non-Hispanic black, 14.6% Hispanic, 5.5% American Indian, and 4.6% Asian; 26.6% were homozygous or heterozygous for APOE-ε4. At the time of cognitive assessment, type 2 diabetes was higher in the placebo group (57.9%; $P < 0.001$) compared with lifestyle (47.0%) and metformin (50.4%). Metformin exposure was higher in the metformin group (8.72 years; $P < 0.001$) compared with placebo (1.43 years) and lifestyle (0.96 years). There were no differences in cognition across intervention arms. Type 2 diabetes was not related to cognition, but higher glycated hemoglobin at year 8 was related to worse cognition after confounder adjustment. Cumulative metformin exposure was not related to cognition.

CONCLUSIONS

Exposure to intensive lifestyle intervention or metformin was not related to cognition among DPPOS participants. Higher glycemia was related to worse cognitive performance. Metformin seemed cognitively safe among DPPOS participants.

There is a large body of literature from observational studies relating type 2 diabetes with higher risk of cognitive impairment, with and without dementia, the worst form of cognitive impairment (1). The association between type 2 diabetes and cognitive impairment has enormous public health implications because one-third of the U.S. adult population has prediabetes or type 2 diabetes (2), and this proportion increases to half of the population over the age of 60 years (3), the group most at risk for cognitive impairment.

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It is not clear whether these relationships are causal and whether the prevention or treatment of type 2 diabetes decreases cognitive impairment. We examined whether diabetes prevention in the Diabetes Prevention Program (DPP), the largest clinical trial of diabetes prevention, was related to long-term cognitive performance. Both lifestyle intervention and metformin decreased the risk of type 2 diabetes compared with placebo among overweight or obese people with impaired glucose tolerance (IGT) and elevated fasting glucose in the DPP (4). DPP participants have continued follow-up in an observational phase called the Diabetes Prevention Program Outcomes Study (DPPOS), and the impact of interventions upon type 2 diabetes incidence has been sustained through 10 years since randomization (5).

We measured cognitive performance in years 8 and 10 of DPPOS (~12 and 14 years after DPP randomization) in order to determine whether prevention and/or delay of type 2 diabetes with metformin and lifestyle intervention in people at high risk for type 2 diabetes was associated with better cognitive performance compared with placebo. Recent studies suggest that metformin may increase the risk of Alzheimer disease (AD) (6,7), and we sought to examine the cognitive safety of metformin. Our primary aim was to compare cognitive performance across the DPP treatment arms in DPPOS. Our secondary aims were to relate glycemia and type 2 diabetes to cognitive performance and to relate cumulative metformin exposure to cognitive performance.

RESEARCH DESIGN AND METHODS

Design

This was an observational study examining several exposures, including the DPP interventions, incident type 2 diabetes, and metformin exposure, in relation to cognitive performance in DPPOS. The eligibility criteria, design, and methods of the DPP (4) and DPPOS (5) have been reported elsewhere. The DPP was a randomized trial of three interventions in 3,234 participants enrolled between 1996 and 1999. The interventions lasted 2.8 years on average. Masked treatment was discontinued in July of 2001, after a reduced incidence of diabetes of 58% was observed in the lifestyle arm and 31% in the metformin arm, compared with placebo. A 13-month bridge period between the DPP and the DPPOS occurred between August 2001 and August 2002. Cognitive function was assessed from July 2009 to October 2010 (year 8 of DPPOS), and from July 2011 to October 2012 (year 10 of DPPOS), ~12 and 14 years after randomization.

Participants

At entry, participants were required to have a BMI $\geq$24 kg/m^2 ($\geq$22 kg/m^2 in Asian Americans), fasting plasma glucose levels between 95 and 125 mg/dL, and IGT (2-h postload glucose of 140–199 mg/dL). People were excluded if taking medications known to alter glucose tolerance or if they had illnesses that could reduce their life expectancy or their ability to participate in the trial. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board.

Study Interventions

The Intensive Lifestyle Intervention (ILS) was a goal-based diet and physical activity intervention designed to achieve and maintain at least 150 min per week of moderate physical activity and reduce weight by 7% from baseline. Participants in the metformin and placebo arms received standard lifestyle recommendations as written information and an annual 20- to 30-min individual session emphasizing the importance of a low-fat diet and regular physical activity to achieve modest weight reduction. Treatment with metformin was increased over 1 month to a full dose of 850 mg taken twice daily. The placebo group received a matching placebo tablet.

All active DPP participants were eligible for continued follow-up into DPPOS: 2,766 of 3,150 (88%) enrolled for a median additional follow-up of 5–7 years; 910 participants were from the ILS, 924 from the metformin arm, and 932 were from the placebo arm. On the basis of the benefits from the ILS in the DPP, all three groups were offered group-implemented lifestyle intervention. Metformin treatment was continued in the original metformin group, with participants unmasked to assignment, and the original ILS group was offered additional lifestyle support.

Measurements

Cognitive Assessments

The cognitive battery measured memory and frontal-executive abilities. All tests were administered in English or Spanish. The measure of memory was the Spanish English Verbal Learning Test (SEVLT) (8). The SEVLT consists of recalling a list of 15 words in three trials of immediate recall and one trial after a distractor list. The total number of correct words recalled after four trials is the outcome reported. The tests of frontal-executive abilities were the total score in the Digit Symbol Substitution Test (DSST) (9) and number of words generated in the animal (10) and letter (11) fluency tests. The DSST is a test in which participants try to match numbers to symbols in 90 s. The total number of correct answers is reported. The animal fluency test asks participants to name as many animals as they can for 1 min. The letter fluency test asks participants for as many words as possible with the letter F in English (P in Spanish) in 1 min. The total number of correct words is reported for the fluency tests. For the primary analyses, we compared total recall of the SEVLT and total correct on word fluency, animal fluency, and DSST among DPP treatment arms. We also constructed a composite cognition measure by converting each of these variables to a standard *z* score with a mean of 0 and an SD of 1 at year 8; *z* scores at year 10 were calculated using the year 8 mean and SDs. The composite *z* score is the mean of the *z* scores for total recall of the SEVLT and total correct of the animal fluency, word fluency, and the DSST.

Other Measures

We compared characteristics at baseline by DPP treatment group among those who underwent cognitive testing in year 8 in order to establish that balance was maintained among those undergoing cognitive testing. Demographic variables included age in years, sex, education in years, and race and ethnic group (white, African American, Hispanic, American Indian, and Asian). Metabolic variables included fasting glucose, glycated hemoglobin (HbA_{1c}), cholesterol, triglycerides, and HDL. HbA_{1c} area under the curve was estimated by averaging all available HbA_{1c} at year 8. All analytical measurements were performed at the DPPOS Central Biochemistry Laboratory (University of Washington, Seattle, WA). Since cognitive scores were not available at the DPP baseline, we compared the following behavioral variables that might be correlated

with cognition: the Short Form Health Survey (SF-36) physical and mental scales, Beck Depression Inventory (BDI), and leisure activity. We also compared type 2 diabetes prevalence and metformin exposure at the time of cognitive assessment.

Incident type 2 diabetes was determined by an annual oral glucose tolerance test and semiannual fasting plasma glucose tests, and required confirmation by a second test, using the criteria of the American Diabetes Association and the World Health Organization. We documented metformin exposure as person-years of taking metformin. We included APOE-ε4 carrier status as a covariate because it is a strong risk factor for cognitive impairment and a potential effect modifier for risk factors (12,13). We genotyped two *APOE* single nucleotide polymorphisms (rs429358 and rs7412) that define APOE genotypes (ε4/ε4, ε4/ε2, ε2/ε4, ε4/ε3, ε3/ε4, ε2/ε2, ε3/ε3, ε2/ε3, and ε3/ε2) in 3,246 DPP participants who had consented to genetic analyses. We used allele-specific primer extension of multiplex amplified products with detection by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry on a Sequenom iPLEX platform. Genotyping success rate was 99.48% and both variants met Hardy-Weinberg equilibrium ($P > 0.05$) in the four ethnic groups with >100 participants. Participants were classified as homozygous (ε4/ε4), heterozygous (ε4/ε2, ε2/ε4, ε4/ε3, and ε3/ε4), and noncarriers (ε2/ε2, ε3/ε3, ε2/ε3, and ε3/ε2) of APOE-ε4.

Statistical Methods

We present quantitative characteristics as mean ± SD and qualitative characteristics as frequencies (%). Continuous variables were compared between two or more groups with the use of the Student *t* test and the ANOVA test, respectively, whereas categorical variables were compared with the use of the χ^2 test of independence. We also used the Student *t* test and ANOVA test to compare the cognitive functions (composite and individual) by treatment group, sex, APOE-ε4, and type 2 diabetes status. Linear regression models were used in analyses requiring covariate adjustment and for testing for interaction effects. Repeated-measures ANOVA was used to test the change of cognitive function from year 8 to year 10 and the effect of metformin use after adjusting for several other covariates such as age, sex, race, and treatment.

RESULTS

The current analysis includes 2,280 participants who underwent cognitive assessments out of a total of 2,344 (97.3%) participants available in year 8 of DPPOS (2009–2010). Supplementary Table 1*A*–*C* shows comparisons of DPP baseline characteristics of the 2,280 participants who underwent cognitive assessments and those from the original DPP participants (n = 3,234) who did not participate, by treatment group. We mention only statistically significant differences. Among participants in the lifestyle group (Supplementary Table 1*A*), those who underwent cognitive testing were older, more likely to be African American, and less likely to be Hispanic. Among participants in the metformin group (Supplementary Table 1*B*), those who underwent cognitive testing were older and had a lower BDI score. Among participants in the placebo group (Supplementary Table 1*C*), those who underwent cognitive testing had lower systolic blood pressure. There were 2,145 cognitive assessments in year 10, 94.07% of those in year 8.

DPP baseline characteristics did not differ substantially among DPP treatment groups (Table 1). The time from randomization to the first cognitive assessment was 12.0 ± 0.8 years and the age at the

Table 1—Characteristics of participants in the DPPOS who underwent cognitive assessments at year 8, 12 years after randomization

Characteristic	Overall (n = 2,280)	Lifestyle (n = 749)	Metformin (n = 776)	Placebo (n = 755)	P value
Age at randomization (years)	51.1 ± 9.9	51.3 ± 10.7	51.5 ± 9.6	50.5 ± 9.5	0.12
Women (%)	1,543 (67.7)	506 (67.6)	513 (66.1)	524 (69.4)	0.39
Education					0.45
≤12 years (%)	564 (24.7)	183 (24.4)	185 (23.8)	196 (26.0)	
13–16 years (%)	1,110 (48.7)	372 (49.7)	367 (47.3)	371 (49.1)	
≥17 years (%)	606 (26.6)	194 (25.9)	224 (28.9)	188 (24.9)	
Race/ethnicity					0.62
White (%)	1,245 (54.6)	402 (53.7)	433 (55.8)	410 (54.4)	
African American (%)	471 (20.7)	150 (20.0)	163 (21.0)	158 (20.9)	
Hispanic (%)	333 (14.6)	107 (14.3)	114 (14.7)	112 (14.8)	
American Indian (%)	126 (5.5)	46 (6.1)	39 (5.0)	41 (5.4)	
Asian (%)	105 (4.6)	44 (5.9)	27 (3.5)	34 (4.5)	
APOE-ε4					0.71
Positive	506 (26.6)	159 (25.4)	171 (26.7)	176 (27.5)	
Negative	1,400 (73.4)	466 (74.6)	469 (73.3)	465 (72.5)	
Fasting glucose (mg/dL)	106.5 ± 8.4	106.2 ± 8.0	106.6 ± 8.6	106.7 ± 8.6	0.56
HbA_{1c}					0.77
%	5.92 ± 0.50	5.92 ± 0.49	5.92 ± 0.50	5.93 ± 0.51	
mmol/mol	41 ± 5.5	41 ± 5.4	41 ± 5.5	41 ± 5.6	
Cholesterol (mg/dL)	203.7 ± 35.3	204.6 ± 35.9	203.5 ± 34.4	203.1 ± 35.6	0.70
Triglycerides (mg/dL)	163.6 ± 95.6	161.6 ± 93.4	159.6 ± 89.1	169.6 ± 103.7	0.10
HDL (mg/dL)	45.9 ± 12.0	46.3 ± 12.5	46.3 ± 11.6	45.1 ± 11.8	0.07
SF-36 mental	54.1 ± 7.2	53.9 ± 7.1	54.2 ± 7.6	54.2 ± 6.8	0.74
SF-36 physical	50.4 ± 7.0	50.7 ± 6.7	50.1 ± 7.2	50.5 ± 7.1	0.25
Systolic blood pressure (mmHg)	123.4 ± 14.7	123.3 ± 14.7	124.0 ± 15.1	122.9 ± 14.4	0.33
Diastolic blood pressure (mmHg)	78.1 ± 9.4	78.3 ± 9.3	78.1 ± 9.6	78.0 ± 9.3	0.89
BDI	4.40 ± 4.36	4.43 ± 4.39	4.34 ± 4.28	4.44 ± 4.44	0.87
Leisure activity (Met-hours)	16.7 ± 25.9	15.8 ± 21.9	16.9 ± 21.7	17.5 ± 32.7	0.41

The values presented are for their time at randomization in the DPP, ~12 years before cognitive assessments. Data are presented for all participants and by DPP randomization arm. Data for continuous variables are presented as mean ± SD. Data for categorical variables are presented as frequency (percentage). P values are from the Pearson χ^2 test for categorical variables and from the ANOVA test for continuous variables.

time of the cognitive assessment was 63.2 ± 9.9 years; these variables did not differ by study arm (Table 2). At the time of the first cognitive assessment, fasting glucose, HbA_{1c} area under the curve, and type 2 diabetes prevalence and duration were lower in the metformin and lifestyle arms compared with the placebo group (Table 2), consistent with the benefits of the interventions documented in DPP (4) and DPPOS (5).

The total number of words recalled in the SEVLT, the total correct answers of the DSST, and the total correct answers in the animal fluency and letter fluency tests were normally distributed. As expected, all scores were lower with older age (Supplementary Table 2). Women performed better in all cognitive tests compared with men (Supplementary Table 3). Cognitive performance was not statistically different among those who were APOE-ε4 carriers compared with noncarriers (Supplementary Table 4). Table 3 shows the comparison of scores in cognitive tests in years 8 and 10 and their difference among the study arms. There were no appreciable or statistically significant differences between the study arms. There was no evidence for effect modification by age-group, sex, type 2 diabetes, or APOE-ε4 in the association between the study arms and cognitive tests as evidenced by nonsignificant interaction terms (Supplementary Table 5). Of particular interest was the association of the DPP arms with cognitive performance in those 60 years or older at randomization, who are most at risk for cognitive impairment. Supplementary Table 2 shows that in addition to the nonsignificant interaction terms for age and DPP arms, there was no appreciable difference in cognitive performance across the intervention arms. For example, the SEVLT scores (total words recalled) were 30.04 ± 9.25, 30.03 ± 9.41, and 31.02 ± 9.78 for the lifestyle intervention, metformin, and placebo arms in people 60 years and older at randomization. The SEVLT scores in people 45–59 years at randomization were 37.26 ± 8.03, 36.81 ± 8.53, and 36.59 ± 8.09 for the lifestyle intervention, metformin, and placebo arms. The SEVLT scores in people younger than 45 years at randomization were 39.97 ± 7.27, 39.95 ± 8.42, and 39.53 ± 7.73 for the lifestyle intervention, metformin, and placebo arms. The comparisons for the DSST, fluency tests, and composite *z* scores show similar results by age-group.

Approximately half of the sample developed type 2 diabetes by year 8 (1,180 participants, 51.8%). Type 2 diabetes was not related to cognitive performance at years 8 or 10 or their difference (Table 4). There was no effect modification by age-group, sex, or APOE-ε4 in the association between type 2 diabetes and cognitive performance. Glycemia examined continuously as HbA_{1c} at year 8 was not related to cognitive tests at years 8 or 10 or their difference in unadjusted models (Supplementary Table 6). However, models adjusted for age, sex, education, and randomization arm revealed statistically significant associations between higher HbA_{1c} and lower cognitive performance in years 8 and 10 in the SEVLT, DSST, animal fluency test, and composite *z* score (Supplementary Table 6). For year 8, the coefficients in the adjusted models were −0.49 for the SEVLT (P = 0.008), −0.78 for the DSST (P = 0.002), −0.24 for animal fluency (P = 0.04), and −0.05 for the composite *z* score (P = 0.001). This change in coefficients and statistical significance was driven by adjustment by age, which was inversely associated with HbA_{1c} (coefficient = −0.03%; $P <$ 0.0001). The adjusted models that excluded age had effect estimates that were not significant, similar to the crude models. These results seem to show negative confounding by age of the association between HbA_{1c} and cognitive performance. This confounding was accounted for in the adjusted models, revealing the inverse association between higher HbA_{1c} and lower cognitive performance.

Last, we examined the relation of metformin use to cognitive performance in all participants, since people in the placebo

Table 2—Characteristics of participants who underwent cognitive assessments, as at year 8 of the DPPOS

Characteristic	Overall (*n* = 2,280)	Lifestyle (*n* = 749)	Metformin (*n* = 776)	Placebo (*n* = 755)	*P* value
Age (years)	63.2 ± 9.9	63.4 ± 10.6	63.5 ± 9.6	62.6 ± 9.5	0.14
Time from randomization (years)	12.0 ± 0.8	12.0 ± 0.8	12.0 ± 0.8	12.0 ± 0.8	0.39
Fasting glucose (mg/dL)	120.2 ± 30.7	120.8 ± 30.4	116.2 ± 27.2	123.7 ± 33.9	<0.001
HbA_{1c}					0.09
%	6.48 ± 1.22	6.58 ± 1.28	6.38 ± 1.11	6.49 ± 1.25	
mmol/mol	47 ± 13.3	48 ± 14.0	46 ± 12.1	47 ± 13.7	
SF-36 mental	53.6 ± 8.9	53.5 ± 8.9	53.7 ± 8.6	53.7 ± 9.1	0.93
SF-36 physical	46.8 ± 9.5	46.9 ± 9.4	46.8 ± 9.6	46.6 ± 9.5	0.85
Systolic blood pressure (mmHg)	120.7 ± 13.9	120.0 ± 13.9	121.1 ± 13.6	121.0 ± 14.1	0.21
Diastolic blood pressure (mmHg)	71.7 ± 9.5	71.4 ± 9.4	71.7 ± 9.7	72.1 ± 9.4	0.38
BDI	4.51 ± 5.04	4.55 ± 5.29	4.49 ± 4.87	4.49 ± 4.97	0.96
Leisure activity (Met-hours)	16.2 ± 19.9	16.9 ± 19.6	15.6 ± 20.5	16.1 ± 19.5	0.47
HbA_{1c} area under the curve					<0.001
%	5.97 ± 0.60	5.93 ± 0.58	5.92 ± 0.57	6.05 ± 0.65	
mmol/mol	42 ± 6.6	41 ± 6.3	41 ± 6.2	4.3 ± 7.1	
Diabetes prevalence (%)	1,180 (51.8)	352 (47.0)	391 (50.4)	437 (57.9)	<0.001
Duration of diabetes (years)	3.70 ± 4.33	2.97 ± 3.90	3.66 ± 4.35	4.46 ± 4.59	<0.001
Time of metformin exposure (years)	3.76 ± 4.70	0.96 ± 2.04	8.72 ± 4.16	1.43 ± 2.51	<0.001

Data for continuous variables are presented as mean ± SD. Data for categorical variables are presented as frequency (percentage). *P* values are from the Pearson χ^2 test for categorical variables and from the ANOVA test for continuous variables.

Table 3—Cognitive function in years 8 and 10 of the DPPOS and their differences by treatment group

Characteristics	Lifestyle (n = 749)	Metformin (n = 776)	Placebo (n = 755)	P value
Total correct for SEVLT				
Year 8	36.41 ± 8.89	36.24 ± 9.33	36.41 ± 8.75	0.91
Year 10	36.89 ± 9.11	37.35 ± 9.39	37.06 ± 9.11	0.63
Difference	0.32 ± 6.31	0.91 ± 6.39	0.57 ± 6.67	0.22
Total correct on DSST				
Year 8	48.92 ± 12.50	48.99 ± 12.84	49.83 ± 12.31	0.30
Year 10	48.84 ± 12.79	49.08 ± 13.40	49.58 ± 12.64	0.54
Difference	−0.14 ± 5.62	0.02 ± 6.30	−0.32 ± 6.08	0.56
Total correct for animal fluency				
Year 8	19.59 ± 5.26	19.60 ± 5.31	19.49 ± 5.25	0.90
Year 10	19.45 ± 5.30	19.60 ± 5.49	19.46 ± 5.32	0.84
Difference	−0.19 ± 4.08	−0.03 ± 4.32	0.00 ± 4.51	0.68
Total correct for letter fluency				
Year 8	13.23 ± 4.59	13.02 ± 4.50	13.15 ± 4.60	0.67
Year 10	13.37 ± 4.74	12.98 ± 4.46	13.12 ± 4.56	0.27
Difference	0.13 ± 3.77	−0.02 ± 3.34	−0.00 ± 3.67	0.71
Composite z score				
Year 8	−0.01 ± 0.78	−0.02 ± 0.77	0.01 ± 0.75	0.86
Year 10	0.01 ± 0.78	0.01 ± 0.80	0.02 ± 0.75	0.99
Difference	0.01 ± 0.38	0.02 ± 0.37	0.01 ± 0.40	0.67

Data are presented as mean ± SD. P values are from the ANOVA test. The tests compared are the SEVLT, the DSST, animal fluency, letter fluency, and a composite z score.

and lifestyle group with incident type 2 diabetes were also exposed to metformin. People in the metformin arm had 8.72 ± 4.16 years of metformin exposure, whereas those in the lifestyle and placebo arms had 0.96 ± 2.04 years and 1.43 ± 2.51, respectively. Years of metformin use was not related to the composite (coefficient = −0.00; P = 0.76), SEVLT (coefficient = 0.04; P = 0.37), DSST (coefficient = −0.07; P = 0.21), animal fluency (coefficient = −0.01; P = 0.74), or letter fluency (coefficient = −0.00; P = 0.85), after adjustment for age, sex, ethnic group, and treatment group. There was modest statistical evidence of effect modification of the association of metformin exposure with cognitive impairment by APOE-ε4 and sex as follows. The interaction term for metformin exposure and APOE-ε4 was significant for the composite (P = 0.042) and DSST (P = 0.041) outcomes. The coefficients relating metformin exposure and the composite were 0.003 (P = 0.54) and −0.012 (P = 0.14) for APOE-ε4 negative and positive, respectively. For the DSST, the coefficients were 0.012 (P = 0.81) for APOE-ε4 negative and −0.289 (P = 0.02) for APOE-ε4 positive. The interaction term for sex and APOE-ε4 with SEVLT as the outcome was significant at P = 0.045. The coefficients relating metformin exposure to the SEVLT were 0.047 (P = 0.56) for men and 0.029 (P = 0.56) for women. Although the interaction terms for APOE-ε4 and sex were significant as previously described, the associations within strata were not appreciable or significant. Thus, it seems reasonable to conclude that there was no effect modification by sex or APOE-ε4 of the association of metformin exposure with cognitive performance.

Table 4—Cognitive function at DPPOS years 8 and 10 and their differences, by diabetes status at year 8

Characteristic	No diabetes (n = 1,100)	Diabetes (n = 1,180)	P value
Total correct for SEVLT			
Year 8	36.51 ± 9.14	36.20 ± 8.85	0.42
Year 10	37.15 ± 9.37	37.07 ± 9.05	0.83
Difference	0.46 ± 6.68	0.74 ± 6.25	0.32
Total correct on DSST			
Year 8	49.23 ± 12.74	49.27 ± 12.38	0.95
Year 10	49.11 ± 13.26	49.22 ± 12.66	0.85
Difference	−0.11 ± 5.82	−0.17 ± 6.18	0.82
Animal correct for word fluency			
Year 8	19.61 ± 5.34	19.51 ± 5.21	0.65
Year 10	19.60 ± 5.54	19.42 ± 5.20	0.45
Difference	−0.04 ± 4.31	−0.10 ± 4.31	0.73
Letter correct for word fluency			
Year 8	13.13 ± 4.65	13.14 ± 4.47	0.94
Year 10	13.17 ± 4.61	13.14 ± 4.56	0.87
Difference	0.05 ± 3.55	0.02 ± 3.63	0.83
Composite z score			
Year 8	0.00 ± 0.78	−0.01 ± 0.75	0.71
Year 10	0.02 ± 0.80	0.01 ± 0.76	0.77
Difference	0.01 ± 0.38	0.01 ± 0.39	0.76

Data are presented as mean ± SD. P values are from the Student t test. The tests compared are the SEVLT, the DSST, animal fluency, letter fluency, and a composite z score.

CONCLUSIONS

Among DPPOS participants who underwent cognitive assessments at year 8, ~12 years after DPP randomization, we found no difference in cognitive performance across DPP arms. This is the first study to examine whether prevention of type 2 diabetes with metformin among overweight or obese people with elevated fasting glucose and IGT is associated with cognitive performance. A cognition ancillary study in the Finnish Diabetes Prevention Study (FDPS) previously examined whether diabetes prevention with a lifestyle intervention among people with IGT was associated with cognitive performance, with similar results (14).

An extensive literature has reported that type 2 diabetes is related to impaired cognition in memory and frontal executive functions, ranging from mild cognitive impairment to dementia (1). This literature has led to the hypothesis that declines in cognitive performance can be prevented by treatment of type 2 diabetes, prevention of type 2 diabetes, or the manipulation of insulin levels (15,16). Our results do not support these hypotheses among people at high risk for type 2 diabetes.

Lifestyle interventions (exercise and diet) are effective treatments for weight loss and improve insulin sensitivity. In the DPP (4) and the FDPS (17), the lifestyle intervention reduced the risk of type 2 diabetes by 58%, associated with reductions in insulin levels (18,19). We found that the lifestyle intervention of DPP was not associated with cognitive performance 12 years after randomization, contrary to our hypothesis. This is consistent with a similar finding in the FDPS, in which no benefit was found for the lifestyle intervention 13 years after randomization (14).

Metformin has several effects that could benefit cognition through cerebrovascular or neurodegenerative mechanisms (20), including decreasing advanced glycation end products (21,22), inflammation (23), coagulation (23), and the prevention of the metabolic syndrome (24). However, recent conflicting data relate metformin to AD, raising questions about its cognitive safety. Metformin increased production of amyloid-β, the culprit of AD, in a cell culture model (25). A case-control study reported that among people with type 2 diabetes, a dementia diagnosis was associated with metformin use (7). Another study found that in people with type 2 diabetes, metformin use was associated with worse cognitive performance (26). These reports conflict with other studies. In an in vitro model of neuronal insulin resistance that was related to greater expression of AD characteristics, metformin prevented the appearance of characteristics of AD (27), and a study in mice showed that metformin decreased AD pathology (28). An epidemiologic study showed that metformin is related to lower AD risk among people with type 2 diabetes (29). A pilot study of metformin in people with mild cognitive impairment showed that metformin treatment improved memory after 12 months compared with placebo (30). Clarifying the cognitive safety of metformin is important because metformin is the medication most commonly used for the treatment of type 2 diabetes, type 2 diabetes prevention, and the treatment for polycystic ovarian disease (31) and is being considered as a therapy for cancer (32,33). Our results suggest that metformin use among people at risk or with type 2 diabetes is cognitively safe.

We found that higher glycemia at the time of cognitive assessment was related to worse cognitive performance in most tests despite finding no association of the DPP interventions and incident type 2 diabetes with cognitive performance. The cognition ancillary study of the FDPS also found that glycemia was related to worse cognitive performance, despite finding no association between the lifestyle intervention and cognitive performance (34). We can only speculate about explanations for this finding. It is possible that the legacy effect (35) of hyperglycemia on cognitive impairment is difficult to reverse, even after prevention of type 2 diabetes. The adverse effects of hyperglycemia on cognition may be resistant to the potential benefits of the metformin and lifestyle interventions, and many years, even decades, may be needed to see a difference in cognitive outcomes. Another possible explanation is that cognitive impairment precedes or accompanies hyperglycemia, that is, that the causal direction is opposite of what we hypothesize (cognitive impairment causes hyperglycemia), or that hyperglycemia and cognitive performance might have other common determinants. We cannot address these scenarios and they require further research.

We must consider threats to validity as potentially explaining the null findings in our study. First, we should consider whether we lacked power to find differences in cognitive performance, either because the instruments used were not sensitive or our sample size was small. We demonstrated that our battery captured small differences between age-groups, such that younger people performed better cognitively. However, it is possible that longer follow-up is necessary to examine differences in cognitive change. Second, we should consider whether confounding explained our results. This seems unlikely because people who underwent cognitive testing were similar in baseline characteristics across treatment groups. Third, we should consider whether bias explains our findings. We reported modest differences between participants who underwent cognitive testing and those who did not in some baseline characteristics that were differential by treatment group, and it is possible that these differences biased the results toward the null.

Our results suggest that delaying the onset of type 2 diabetes with metformin and lifestyle among those with high fasting glucose and IGT does not benefit cognitive performance, but we must consider alternative explanations for these findings. The differences in diabetes and glycemia between the intervention arms at the end of DPP were appreciably smaller at the time of cognitive assessments. Perhaps larger sustained differences in glycemia, such as the ones observed at the end of DPP, would be necessary to observe cognitive effects. Last, it is important to point out two salient characteristics of the DPPOS cohort that may have resulted in null findings. First, it was comprised of people at high risk for type 2 diabetes, and second, it had an average age of 63 years at the time of cognitive assessment. It is possible that people at high risk for type 2 diabetes are similar metabolically to people who meet early criteria for type 2 diabetes, particularly in DPP/DPPOS, in which participants were tested every 6 months with fasting glucose and every year with oral glucose tolerance tests for development of type 2 diabetes. This may explain the observation of no differences in cognitive performance between people with and without type 2 diabetes. Larger samples sizes may be needed to detect small differences in cognition, or a longer follow-up may be needed because of the legacy effect (35). In terms of age, DPPOS participants were examined on average at an age when the risk of cognitive impairment starts to increase, and it is possible that differences in cognition among the groups will present when tested at older ages. However, we showed that our findings were similar across age-groups. Cognitive performance across the DPP treatment arms was virtually identical in year 8, but there were small nonsignificant differences in memory performance as measured by the SEVLT in year 10, and in the differences between years 8 and 10, that modestly favored the metformin arm. These nonsignificant differences may be due to chance, but it is possible that longer follow-up could show further separation in cognitive performance between the treatment arms.

Our study has some limitations. DPP did not collect cognitive information at baseline. However, cognitive differences between the groups at baseline seem unlikely because participants were similar in demographic, metabolic, and behavioral variables. Another limitation is the lack of subclinical markers of cognitive

impairment. It is possible that the DPP interventions resulted in effects on brain structure and pathology not evident in cognitive testing. An example of this potential scenario was observed in the cognitive study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD-MIND). ACCORD-MIND reported that the intensive glycemic control arm did not demonstrate a cognitive benefit but this treatment arm showed less decrease in brain volume (36), suggesting a benefit on brain neurodegeneration, one of the mechanisms underlying cognitive impairment.

In conclusion, prevention of type 2 diabetes with lifestyle and metformin was not related to better cognitive performance 12 years after randomization in a mostly middle-aged sample of people with IGT, but worse glycemia at the time of cognitive testing was related to worse cognitive performance. Our data suggest that metformin is safe from a cognitive standpoint.

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