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Relation of Type 2 Diabetes With Cognitive Change in a Multiethnic Elderly Cohort

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Abstract

OBJECTIVES—Diabetes may raise dementia risk. However, the pattern of cognitive change over time in non-demented older adults with diabetes, including the onset of cognitive decline, is unclear. We examined the association of diabetes and cognitive functioning at baseline and cognitive change over time in a large, ethnically diverse sample of older adults.

DESIGN—Prospective cohort study.

SETTING—Washington Heights-Inwood Columbia Aging Project (WHICAP), a community-based, prospective study of risk factors for dementia.

PARTICIPANTS—1,493 met both inclusion and exclusion criteria for this study.

MEASUREMENTS—Participants underwent baseline and follow-up cognitive and health assessments approximately every 18 months. Generalized estimating equations were used to examine the longitudinal association between diabetes and cognition.

RESULTS—Diabetes was associated with poorer baseline cognitive performance in memory, language, processing speed/executive functioning, and visuospatial abilities. After adjusting for age, education, sex, race/ethnicity, and apolipoprotein-ε4, participants with diabetes performed significantly worse at baseline relative to those without diabetes in language and visuospatial abilities. There were no differences between those with and without diabetes in terms of rate of cognitive change over a mean follow-up time of six years.

CONCLUSION—The rate of cognitive change in elderly persons with and without diabetes is similar, although cognitive performance is lower in persons with diabetes. Our findings suggest that cognitive changes may occur early during the diabetes process and highlight the need for studies to follow participants beginning at least in midlife, prior to the typical later-life onset of dementia.

Keywords

Diabetes; cognition; aging; vascular risk factors

INTRODUCTION

Approximately 27% of adults aged 65 years or older in the United States are estimated to have type-2 diabetes. If pre-diabetes is also considered, the estimated prevalence rate increases to 50%[1]. It seems clear that diabetes is associated with a higher risk of clinical

dementia including vascular dementia and Alzheimer's disease (AD)[2–4], but the mechanisms remain unclear. Diabetes is related to a higher risk of cerebral infarcts[5,6], but evidence for its association with AD neuropathology (i.e., amyloid plaques and neurofibrillary tangles [NFT]) is conflicting [5–9]. It remains unclear whether diabetes increases risk for AD neuropathology or solely lowers the threshold to manifest dementia through cerebrovascular disease[2,10].

There is growing interest in the role of vascular risk factors such as diabetes in cognitive decline short of dementia. Several cross-sectional studies have reported that older adults with diabetes show decrements across a variety of cognitive domains including memory, language, processing speed, executive functioning, and visuospatial abilities[11–17]. Less is known about how these cognitive changes evolve over time. Results from longitudinal studies have been mixed with some studies showing that cognitive decline among older adults with diabetes exceeds the effects of normal aging[18–22] whereas other studies have not found evidence of accelerated cognitive decline in diabetes[23–25]. Notably, many of these longitudinal studies have used very limited testing and included global cognitive screening measures[18,21,22], which have been criticized for poor sensitivity[26,27].

We addressed the question of how diabetes affects cognitive trajectories by examining the cross sectional and longitudinal association of diabetes with cognition in an ethnically diverse, well-characterized sample with comprehensive neuropsychological data. Given that previous studies suggest that diabetes is associated with increased risk of mild cognitive impairment[28] and dementia[4], we hypothesized that diabetes is associated with steeper decline in performance in all cognitive domains.

METHODS

Participants

Participants for these analyses were from the Washington Heights-Inwood Columbia Aging Project (WHICAP) cohort recruited between 1999 and 2001. WHICAP is a community-based, prospective study designed to identify dementia predictors. A sample of non-demented Medicare recipients aged 65 years or older from three contiguous ZIP codes in northern New York City were invited to participate[29–31]. Briefly, invitations were mailed to 7,120 individuals from households with known telephone numbers. Among these, 265 (3.7%) had died, 1,541 (21.6%) no longer lived in the area, 662 (9.3%) were ineligible, and 2,810 (39.5%) refused participation. Individuals who reported a dementia diagnosis were excluded. The sample recruited included 2,184 individuals, with a recruitment rate among eligible individuals of approximately 40%. Among these 2,184 participants, we excluded those with missing diabetes information (n = 24), prevalent dementia (n = 217 including 159 individuals [73.3%] without diabetes and 58 individuals [26.7%] with diabetes) or missing dementia diagnosis information (n = 2), and no follow-up (n = 448). Reasons for no follow-up included refusal (n=136, 30.4%), unable to contact (n=104, 23.2%), death (n=97, 21.7%), move (n=43, 9.6%), and unable to schedule (n=68, 15.2%). The final analytic sample comprised 1,493 participants (Figure 1). This study was approved by the New York Psychiatric Institute Institutional Review Board. All participants provided written informed consent.

Assessment Procedures

Participants underwent baseline and follow-up interviews including medical and psychiatric history; physical examination; phlebotomy; and comprehensive neuropsychological assessments[32]. Follow-up interviews occurred approximately every 18 months. The mean follow-up time across the entire sample was 6.05 years (standard deviation=3.02; range=1.14–12.09). Follow-up data up to 2012 were included in these analyses.

Diabetes and Demographic and Vascular Risk Covariates

Demographic variables including age, education, and race/ethnicity using the format of the 1990 census were determined by self-report. Diabetes was identified by self-report or by use of diabetes medications at baseline or during follow-up. History of stroke, hypertension, and smoking, were determined by self-report or clinical history. Plasma total cholesterol level was obtained using standard enzymatic techniques. High density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid[33]. Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL. High-sensitivity C-reactive protein (CRP) level was measured using an ultra-sensitive enzyme-linked immunosorbent assay. Apolipoprotein E (APOE) genotyping was obtained using a polymerase chain reaction based method. Participants were classified as APOE-ε4 carriers if they had at least one ε4 allele.

Neuropsychological Assessment

The neuropsychological battery was designed to assess a broad range of cognitive abilities including memory, language, processing speed/executive functioning, and visuospatial abilities[32]. Specific tests included for each domain were: memory (Selective Reminding Test [SRT] total recall, delayed recall, and delayed recognition), language (modified 15-item Boston Naming Test total score, Letter Fluency total, Category Fluency total, Similarities subtest of the Wechsler Adult Intelligence Scale – Revised, Boston Diagnostic Aphasia Evaluation Repetition and Comprehension subtests), processing speed/executive functioning (Color Trails 1 and 2), and visuospatial abilities (Benton Visual Retention Test [BVRT] recognition and matching tests, Rosen Drawing Test, Identities and Oddities subtest of the Mattis Dementia Rating Scale). Table 2 presents possible ranges and descriptive statistics (means and standard deviations for those with and without diabetes separately) as well as results from linear regression examining the association between diabetes and cognitive performance for these individual measures. Participants were tested in either English or Spanish depending on their preferred language.

For this study we examined a composite score developed for the WHICAP sample constructed for each cognitive domain using factor analysis[34]. Methods used to create the composite scores used in the current study have been previously described[34]. Briefly, to identify the underlying factor structure, exploratory factor analysis (EFA) using principal axis factoring and oblique rotation was conducted on the 15 cognitive measures in the English speaking sample only. The number of factors to retain was determined by several methods including visual inspection of the scree plot, adherence to the Kaiser eigenvalue >1 rule, and inspection of the factor solution to ensure that the factors were interpretable and consistent with prior research in different samples. Four factors were derived from the EFA:

memory, language, processing speed, and visuospatial ability. The model from the EFA was then converted to a confirmatory factor analysis (CFA) in which each variable loaded only on the factor with the highest loading. CFA demonstrated that the four-factor model fit the data well in the English and Spanish samples and across the entire sample. The fit of three- and five-factor models across the English speakers, Spanish speakers, and entire sample demonstrated the four-factor model was the best-fitting model within each sample. For all factor scores, a higher score reflects better performance.

Invariance analyses are statistical tools that allow researchers to assess whether variables of interest represent the same theoretical constructs across groups. The establishment of measurement invariance indicates that test scores measure the same psychological constructs across diverse groups. It is crucial to establish equivalence of neuropsychological constructs used to characterize cognitive decline and dementia across diverse cultural and linguistic groups. A previously published report applying invariance analyses to the WHICAP sample indicated that scores on the neuropsychological tests are assessing similar constructs across English and Spanish speakers[34].

Statistical Analyses

We conducted 3 types of analyses. First, we conducted bivariate analyses comparing baseline participant characteristics between those with and without diabetes. Second, we compared the baseline scores and follow-up scores on individual cognitive measures that comprised the composite cognitive scores between participants with and without diabetes. Third, we related diabetes status to changes in the composite z scores during follow-up using repeated measures analyses.

For the bivariate analyses, analysis of variance (ANOVA) for continuous variables, χ^2 tests for categorical variables, and a Mann-Whitney U test for CRP were performed to compare participants with and without diabetes in terms of demographic, vascular risk, and cognitive variables. Tukey's post-hoc tests were conducted for comparison of the participants with and without diabetes in terms of racial/ethnic group.

For the analyses relating diabetes status to the individual components of the composite cognitive scores, we used linear regression to estimate the difference between the means for participants with and without diabetes. We also calculated Cohen's d in order to provide an estimate of effect size[35]. Cohen's d of 0.2, 0.5, and 0.8 are considered small, moderate, and large effect sizes, respectively[35].

For the repeated measures analyses relating diabetes status to changes in the composite cognitive scores generalized estimating equations[36] (GEE) were used to model the relationship over time of participant group (with versus without diabetes) and cognitive performance. GEE is a statistical method that allows the examination of repeated correlated data across individuals, in this case, repeated cognitive scores. This type of analysis is different from that in which there is a single outcome measure per individual (e.g., when examining mortality or dementia onset). Our data had multiple repeated cognitive outcome measures per individual that are not independent of each other, and GEE takes this into account. The variables of interest from a GEE model output include time (years from

baseline), group (with versus without diabetes) and the time x group interaction. A significant group effect indicates a difference between the groups at the baseline evaluation, with a negative regression coefficient indicating that those with diabetes had poorer cognitive performance than those without diabetes. A significant time effect indicates a change of test scores over time, with a negative regression coefficient indicating worsening scores over time regardless of diabetes status. A significant group × time regression coefficient indicates that the change in scores over time is different for the two groups. A negative regression coefficient indicates that individuals with diabetes had a relative decline compared with those without diabetes.

We performed GEE analyses using three sets of models: 1) unadjusted model with no covariates; 2) adjusted model with demographic and genetic variables that are risk factors for cognitive decline in the WHICAP cohort including age at baseline, years of education, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and APOE-ε4 genotype as covariates; and 3) adjusted model with the risk factors for cognitive decline from the second model and vascular risk factors that co-occur with diabetes and predict cognitive impairment[37,38] as covariates. These vascular risk factors included stroke, hypertension, HDL and non-HDL cholesterol levels, CRP, and current smoking, all predictors of cognitive impairment in our sample[37–39]. Because these vascular factors may share the causal pathway between diabetes and cognitive impairment, attenuation of associations after the addition of these covariates should be interpreted as evidence of mediation, not confounding. This third model was run in order to examine whether the association of diabetes with cognitive impairment was independent of vascular mechanisms. Significance levels of 0.05 were used for all tests. All analyses were performed using SPSS (version 19).

RESULTS

We excluded 691 participants from the analytic sample due to missing diabetes information, prevalent dementia, or no follow-up. Compared to participants in the analytic sample, those excluded were older at baseline (mean age of 78.95 ± 7.85 versus 76.04 ± 6.46 years); less educated (8.89 ± 4.81 versus 10.88 ± 4.76 years of education); were more likely to be Black, Hispanic, and APOE-ε4 carriers; and had lower memory, language, processing speed/executive functioning, and visuospatial composite scores. There was no difference between the sample participants and those who attended the baseline exam but were excluded from the present study in terms of prevalence of diabetes (Supplemental Table S1).

Compared to those without diabetes, individuals with diabetes were younger; less educated; less likely to be white and APOE-ε4 carriers; and more likely to have hypertension, stroke, higher CRP levels, and lower HDL and non-HDL cholesterol levels (Table 1). Participants with diabetes had significantly lower composite scores of language, processing speed/executive functioning, and visuospatial abilities at baseline relative to those without diabetes. Participants with diabetes also had lower composite memory scores at baseline compared to those without diabetes but this difference was not statistically significant ($p = 0.10$). There was no difference between those with and without diabetes in terms of length of follow-up.

When the 15 individual cognitive measures included in the composite scores were examined separately with linear regression, diabetes was associated with significantly poorer baseline performance on 13 of the 15 measures including measures of memory, language, processing speed/executive functioning, and visuospatial abilities (Table 2). At each participant's final follow-up (a mean of approximately 6 years after baseline), diabetes was associated with significantly poorer performance on 10 of the 15 cognitive measures including measures of language, processing speed/executive functioning, and visuospatial abilities. In general, the magnitude of differences in mean scores between those with and without diabetes at baseline and follow-up was generally small (Cohen's d values, which are an effect size measure indicating the difference in means in standard deviation units, ranged from .01 to .35).

Unadjusted GEE models demonstrated that participants with diabetes performed significantly worse at baseline relative to those without diabetes in memory, language abilities, processing speed/executive functioning, and visuospatial abilities (Table 3). After adjusting for risk factors for cognitive decline including age at baseline, years of education, sex, race/ethnicity, and APOE-ε4 genotype (Model 2), participants with diabetes performed significantly worse at baseline relative to those without diabetes in terms of language and visuospatial abilities with a trend toward poorer performance on processing speed/executive functioning. After adjusting for additional vascular risk factors (stroke, hypertension, HDL and non-HDL cholesterol levels, CRP level, and smoking), results remained qualitatively and statistically similar to Model 2, which adjusted for demographic and genetic risk factors.

Across the entire sample of participants with and without diabetes, there was significant decline in memory and processing speed/executive functioning over time using unadjusted models. Both adjusted models showed decline in processing speed/executive functioning but improvement in language abilities over time. See Table 3.

When the interaction between time and diabetes status was assessed, there was no significant difference between participants with and without diabetes in terms of rate of change in any of the cognitive abilities assessed as indicated by a non-significant interaction term for diabetes and time across all models (Table 3). However, although the rates (slopes) of change in memory, language, speed/executive functioning, and visuospatial abilities were similar for persons with and without diabetes, persons with diabetes performed consistently worse over time such that the slope of performance for persons with diabetes was similar in rate but lower in performance than for those without diabetes (Figure 2, Table 3).

We conducted secondary GEE analyses among those without incident dementia examining the association of diabetes with cognitive change to ensure that the results were not biased by the inability of persons with dementia to undergo proper neuropsychological testing. These analyses showed results similar to those described above (Supplementary Table S2).

DISCUSSION

Diabetes was associated with worse baseline cognitive performance on all cognitive domains including memory, language, processing speed/executive functioning, and visuospatial abilities. In general, the sizes of the differences were small. After adjusting for

demographic variables and APOE-ε4 genotype, diabetes was significantly associated with worse baseline language and visuospatial performance, and an association with poorer processing speed/executive functioning that was close to statistical significance. After adjusting for vascular predictors of cognitive impairment, findings remaining qualitatively and statistically similar, suggesting that results were not mediated by vascular disease. However, diabetes was not associated with rate of change in any cognitive domain. These findings are contrary to our hypothesis that diabetes is associated with steeper cognitive decline. Potential explanations for the finding of poorer performance but equal rates of change include that separation of slopes occurred earlier in life (e.g., during middle age), that diabetes causes an insult or a state that causes lower cognitive performance without accelerated decline, that a third factor related to diabetes such as lower cognitive reserve explains this finding, or that diabetes and cognitive decline are somehow co-occurring but are not causally related.

Our findings are consistent with evidence from previous studies of older adults showing that diabetes is associated with worse cognitive performance but not accelerated cognitive decline[23–25,40]. Studies in middle-aged adults diagnosed with diabetes suggest that cognitive decrements likely begin during the pre-diabetic stages and progress slowly[17,25,41,42]. Neuroimaging studies show that diabetes is associated with lower brain volumes but not brain atrophy[43], paralleling the findings for cognitive performance. Although several studies suggest that the cognitive trajectories of most older adults with diabetes do not substantially differ from those seen in normal aging [44], other studies have shown accelerated cognitive aging in diabetes [18–22].

Diabetes is associated with higher dementia risk[3,4], but the underlying mechanisms remain uncertain. Diabetes increases the risk of cerebral infarcts[5,6], but its association with AD neuropathology is less clear and studies are conflicting[6–95]. Evidence from autopsy studies suggests that vascular and AD pathologies may have an additive effect on cognitive impairment [10,45] raising the possibility that those with diabetes who may be at risk for vascular pathologies require less AD pathology to reach a threshold where cognitive impairment manifests itself clinically. It is possible that diabetes may lead to lower resilience to AD pathology due to increased cerebrovascular burden, increasing the risk of clinical diagnosis of AD or other dementia. In addition, individuals with diabetes have lower educational attainment that may be related to lower cognitive reserve[46] that may further decrease resilience to AD pathology in addition to cerebrovascular disease. Our results suggest that the association of diabetes with cognitive performance is at least partially independent of cerebrovascular factors, and this association could be accounted for by less cognitive reserve, neurodegenerative mechanisms, or other unknown mechanisms.

The onset of cognitive changes related to diabetes is not clear. One view proposes that there are two crucial periods of life during which diabetes-related cognitive decrements occur: early in life during brain development and later in life when age-related neurodegenerative changes occur, often at age 65 or older[47]. However, middle age may also be a critical time point, when the prevalence of diabetes and prediabetes increases. It is possible that our elderly sample did not provide the opportunity to detect the point when the separation of

slopes of change in cognitive performance between persons with and without diabetes occurred, and that the study of younger cohorts is necessary for this purpose.

The finding that slopes of cognitive change are similar in persons with and without diabetes is not inconsistent with previous findings of increased incident MCI[48] and dementia[4,31,37]. Although we show that the slopes of cognitive decline are similar for persons with and without diabetes, cognitive performance is consistently lower for persons with diabetes, explaining how persons with diabetes reach thresholds for MCI and dementia diagnoses sooner than persons without diabetes. Our current finding that diabetes is related to lower performance in all cognitive domains is also consistent with our previous findings relating diabetes to both amnestic and non-amnestic cognitive syndromes, including amnestic and non-amnestic MCI,[48] and Alzheimer's and vascular dementia[4,31,37].

The primary strengths of the present study include the detailed longitudinal cognitive assessment and the large, ethnically diverse sample. The latter is particularly important in light of evidence that prevalence of cognitive impairment and dementia attributable to diabetes is higher in blacks and Hispanics than in whites[49]. However, the present study has limitations that include ascertainment of diabetes and other vascular risk factors (e.g., hypertension) by self-report and/or medication use. As a result, we may not have captured individuals with undiagnosed pre-diabetes, diabetes or hypertension, which may underestimate the effects of these conditions on cognition. In addition, we cannot rule out practice effects, regression to the mean, or unmeasured or residual confounding that may have influenced the observed pattern of results. Given that individuals with diabetes had significantly less education relative to those without diabetes, it is possible that they had less experience with test-taking and strategies for maximizing test performance. These individuals may have the most to gain from practicing the cognitive tests[50]. However, notably, a recent study demonstrated that retest effects do not differ by vascular risk burden in the WHICAP sample[50]. Also, there is potential selection bias due to attrition related to diabetes morbidity and mortality. Furthermore, we did not assess the course or severity of diabetes and did not examine diabetes treatment or complications.

Findings from the present study and previous studies suggest that cognitive changes occur relatively early during the diabetes process. As the global prevalence of diabetes continues to increase, the number of dementia cases attributable to diabetes is also expected to increase. Given that interventions that treat or prevent diabetes could serve as potential interventions to prevent or postpone the development of cognitive decline and dementia, a better understanding of the evolution of cognitive changes associated with diabetes is necessary.

CONCLUSION

In the present study diabetes was associated with significantly worse baseline cognitive performance on all cognitive domains we studied including memory, language, processing speed/executive functioning, and visuospatial abilities in a sample of ethnically diverse older adults. However, there were no significant differences between those with and without diabetes in terms of rate of change in any of these domains. Future longitudinal studies need

to examine younger age groups with ascertainment of pre-diabetes and continuous measures of glycemia such as HbA1c incorporating clinical, genetic, and neuroimaging data in order to better understand the mechanisms by which diabetes and pre-diabetes affect cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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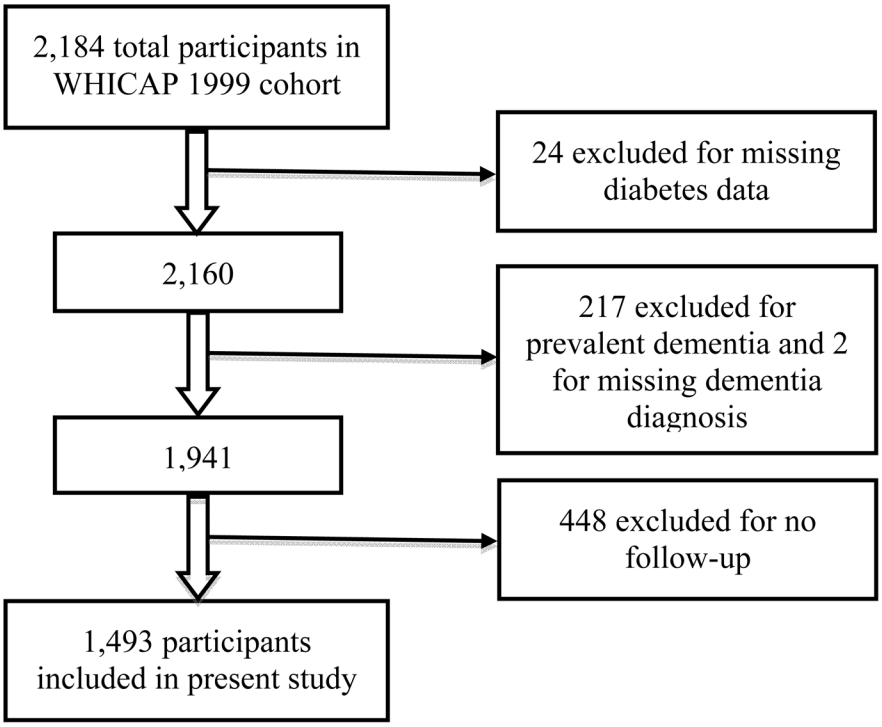

Figure 1.
Flow chart showing participant selection process

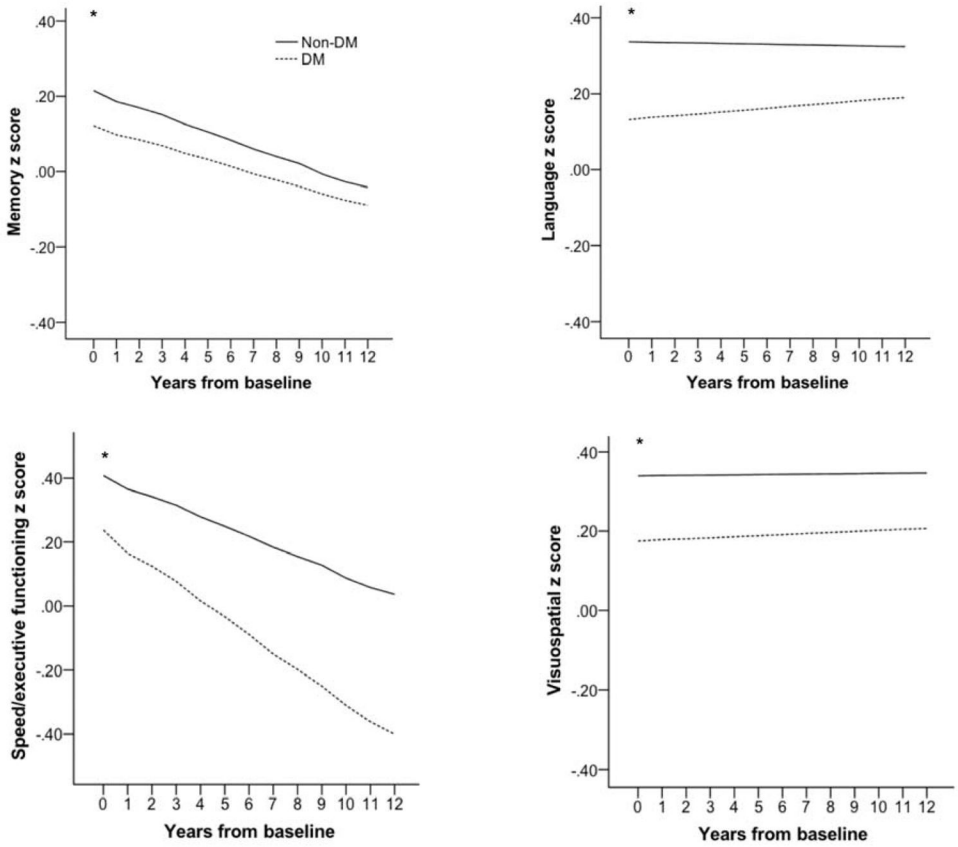

Figure 2.

Regression (GEE predicted z scores from adjusted models) of change in performance in memory, language, processing speed/executive functioning, and visuospatial abilities by diabetes mellitus status from unadjusted models.

* Older adults with diabetes performed significantly more poorly at baseline relative to those without diabetes ($p < .05$).

Table 1

Baseline participant characteristics by diabetes status

	Non-diabetes mean (± SD)	Diabetes mean (± SD)	F, χ^2, or U	p≠
N	1115	378		
Age (years)	76.3 (± 6.7)	75.4 (± 5.8)	5.01	0.03
Education (years)	11.2 (± 4.7)	9.9 (± 4.8)	21.88	<0.001
Sex (% women)	67.5	66.6	0.10	0.76
Ethnic group (%)				<0.0001
Non-Hispanic white	36.4	22.2		
Non-Hispanic black	31.4	34.4	13.93	<0.001 (vs. white)
Hispanic	31.0	39.9	23.84	<0.001 (vs. white)
Other	1.2	3.4	17.46	<0.001 (vs. white)
APOE genotype (% ε4 carrier)	27.4	20.7	5.61	0.02
Current smoker (%)	10.5	10.1	0.04	0.84
Hypertension history (%)	73.7	85.2	14.60	<0.001
Stroke history (%)	13.7	21.3	8.73	0.003
CRP, median (interquartile) mg/L†	5.0 (2.7–13.4)	7.4 (3.8–19.3)	U=88973.00 Z=−3.19	<0.001
HDL*	49.5 (± 14.9)	45.0 (± 13.1)	19.80	<0.001
Non-HDL cholesterol*	152.1(± 36.8)	146.6 (± 37.4)	4.54	0.03
Baseline memory Z score	0.31 (± 0.71)	0.24 (± 0.65)	2.67	0.10
Baseline language Z score	0.36 (± 0.62)	0.15 (± 0.61)	32.33	<0.001
Baseline speed/executive function Z score	0.43 (± 0.79)	0.22 (± 0.89)	11.69	0.001
Baseline visuospatial Z score	0.36 (± 0.56)	0.19 (± 0.62)	24.61	<0.001
Follow-up time (years)	6.05 (± 3.02)	6.05 (± 3.06)	<.0001	0.99

SD = standard deviation; APOE = apolipoprotein E; CRP = C-reactive protein; HDL = high-density lipoprotein

*Based on 1135 participants. 358 participants were excluded from the analysis due to missing data on lipids information.

†Based on 1060 participants. 433 participants were excluded from the analysis due to missing CRP data.

≠P-values from Chi-squared test for categorical variables, from Mann-Whitney U test for CRP, and from analysis of variance (ANOVA) for all other continuous variables.

Table 2

Descriptive statistics and linear regression results for association between diabetes and performance on individual neuropsychological measures at baseline and final follow-up

		Baseline						Follow-up					
Variable	**Possible Range**	**Non-diabetes mean (± SD)**	**Diabetes mean (± SD)**	**B**	**SE**	**Cohen's d**	**p**	**Non-diabetes mean (± SD)**	**Diabetes mean (± SD)**	**B**	**SE**	**Cohen's d**	**p**
N		1115	378					1115	378				
Memory													
SRT-total recall	0–72	38.24 (±10.45)	36.87 (±9.83)	−1.36	0.62	0.13	.028	34.28 (±11.55)	32.87 (±11.27)	−1.42	0.76	0.12	.061
SRT-delayed recall	0–12	5.56 (±2.63)	5.38 (±2.42)	−0.17	0.16	0.07	.275	4.46 (±2.89)	4.25 (±2.62)	−.023	0.19	0.07	.255
SRT-delayed recognition	0–12	11.14 (±1.44)	11.06 (±1.37)	−0.07	0.09	0.06	.390	10.16 (±2.37)	10.17 (±2.11)	<.001	0.15	0.01	.998
Language													
Naming total	0–15	13.66 (±1.73)	13.37 (±1.78)	−0.29	0.11	0.17	.007	13.47 (±1.94)	13.39 (±1.98)	−0.09	0.13	0.04	.504
Letter fluency mean (# of words)	0+*	10.07 (±4.42)	8.66 (±4.02)	−1.41	0.26	0.33	<.001	9.77 (±6.13)	8.67 (±6.19)	−1.11	0.41	0.18	.007
Category fluency mean (# of words)	0+*	14.78 (±4.29)	13.77 (±4.05)	−1.01	0.26	0.24	<.001	13.03 (±4.43)	12.25 (±4.10)	−0.77	0.29	0.18	.007
Similarities	0–28	11.98 (±7.32)	9.53 (±7.08)	−2.48	0.43	0.34	<.001	11.81 (±7.63)	9.58 (±7.18)	−2.25	0.49	0.30	<.001
Repetition	0–8	7.68 (±0.69)	7.59 (±0.76)	−0.09	0.04	0.13	.031	7.37 (±1.11)	7.33 (±1.11)	−0.04	0.07	0.04	.560
Comprehension	0–6	5.28 (±1.07)	5.07 (±1.20)	−0.21	0.07	0.19	.002	5.05 (±1.25)	4.75 (±1.39)	−0.30	0.09	0.23	<.001
Visual-spatial													
BVRT recognition	0–10	7.04 (±2.17)	6.60 (±2.23)	−0.45	0.13	0.20	.001	6.80 (±2.26)	6.29 (±2.31)	−0.52	0.16	0.22	.001
BVRT matching	0–10	8.69 (±1.81)	8.35 (±1.99)	−0.35	0.11	0.18	.002	8.51 (±1.84)	8.04 (±1.99)	−0.47	0.13	0.25	<.001
Rosen	0–5	2.66 (±0.95)	2.38 (±1.09)	−0.27	0.06	0.28	<.001	2.41 (±1.11)	2.25 (±1.15)	−0.16	0.08	0.14	.032
Identities/Oddities	0–16	14.52 (±1.75)	14.15 (±1.91)	−0.38	0.11	0.21	.001	14.54 (±1.83)	14.23 (±2.00)	−0.30	0.13	0.17	.020
Processing speed													
CTT 1 (seconds)	<360	94.60 (±46.85)	105.38 (±52.94)	10.67	3.57	0.22	.003	108.85 (±62.54)	123.17 (±67.10)	14.30	4.69	0.22	.002
CTT 2 (seconds)	<360	158.18 (±52.00)	169.19 (±54.82)	10.87	4.04	0.21	.007	182.85 (±73.94)	209.17 (±80.19)	26.21	6.03	0.35	<.001

SRT = Selective Reminding Test; BVRT = Benton Visual Retention Test

B, standard error, and p values are from linear regressions with diabetes as the predictor variable and cognitive score as the dependent variable. B (unstandardized coefficient) is equal to the difference in mean scores between those with and without diabetes. Cohen's d of 0.2, 0.5, and 0.8 are considered small, moderate, and large effect sizes, respectively[35]. Hierarchical linear regression models

demonstrated that, after adjusting for age and education, diabetes was associated with significantly poorer baseline performance on measures of language (Letter Fluency: B ± SE = −.89 ± .22, p < .001; Category Fluency: B ± SE = −.61± .22, p = .007; Similarities: B ± SE = −1.26 ± .33, p < .001) and visuospatial abilities (Rosen: B ± SE = −.19 ± .06, p = .001; Identities/Oddities: B ± SE = −.22 ± .10, p = .029) with trends toward poorer performance on executive functioning/processing speed (Color Trails 1: B ± SE = 5.74 ± 3.12, p = .066; Color Trails 2: B ± SE = 6.34 ± 3.57, p = .076). After adjusting for age and education, diabetes was associated with poorer follow-up performance on measures of language (Similarities: B ± SE = −1.02 ± .39, p = .009) and executive functioning/processing speed (Color Trails 1: B ± SE = 9.30 ± 4.41, p = .035; Color Trails 2: B ± SE = 20.55 ± 5.69, p < .001) with trends toward poorer performance on additional measures of language (Category Fluency mean: B ± SE = −.44 ± .26, p = .082; Comprehension: B ± SE = −.15 ± .08, p = .052); and visuospatial abilities (Benton Matching: B ± SE = −.20 ± .12, p = .089).

*Participants are asked to generate as many words as they can that begin with each letter or category (e.g., animals) in 60 seconds (within specific guidelines). Mean number of correct words named across the three letters or categories are displayed.

†The Color Trails test (CTT) requires participants to connect numbers (CTT 1) or numbers alternating in the same color (CTT 2) in the correct order as quickly as possible. Higher scores indicate slower speeds (i.e., worse performance).

Table 3

GEE models of cognitive performance at baseline and over time as a function of diabetes status

	Memory		Language		Processing speed/executive functioning		Visuospatial	
Model 1: Unadjusted	B	p	B	p	B	p	B	p
Diabetes (Yes vs. No)	−0.094	0.031	−0.205	<0.001	−0.170	0.003	−0.165	<0.001
Time (year)	−0.022	<0.001	−0.001	0.738	−0.032	<.001	0.001	0.830
Diabetes X Time	0.004	0.634	0.006	0.386	−0.023	0.095	0.002	0.741
Model 2: Adjusted for age, education, sex, ethnicity, and APOE genotype	B	p	B	p	B	p	B	p
Diabetes (Yes vs. No)	−0.020	0.603	−0.090	0.004	−0.087	0.102	−0.080	0.004
Time (year)	0.002	0.626	0.008	0.015	−0.021	0.001	0.006	0.056
Diabetes X Time	0.010	0.217	0.010	0.098	−0.011	0.383	0.008	0.164
Model 3: Adjusted for age, education, sex, ethnicity, APOE genotype, and vascular risk factors*	B	p	B	p	B	p	B	p
Diabetes (Yes vs. No)	−0.052	0.276	−0.077	0.046	−0.130	0.052	−0.084	0.015
Time (year)	0.002	0.657	0.008	0.037	−0.022	0.006	0.005	0.171
Diabetes X Time	0.015	0.129	0.013	0.079	−0.008	0.617	0.009	0.177

All predictors were simultaneously included in each GEE model.

APOE = apolipoprotein E

*Model adjusted for age, education, sex, ethnicity, APOE genotype (APOE ε4 carrier versus noncarriers), vascular risk factors (history of stroke, hypertension, high density lipoprotein [HDL] and non-HDL cholesterol levels, and smoking) and C-reactive protein level