Cognitive decline following incident and preexisting diabetes mellitus in a population sample

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ABSTRACT

Objective: To examine if incident and preexisting diabetes mellitus (DM) were associated with cognitive decline among African Americans (AAs) and European Americans (EAs).

Methods: Based on a prospective study of 7,740 older adults (mean age 72.3 years, 64% AA, 63% female), DM was ascertained by hypoglycemic medication use and Medicare claims during physician or hospital visits, and cognition by performance on a brief battery for executive functioning, episodic memory, and Mini-Mental State Examination (MMSE). Decline in composite and individual tests among those with incident DM, with preexisting DM, and without DM was studied using a linear mixed effects model with and without change point.

Results: At baseline, 737 (15%) AAs and 269 (10%) EAs had preexisting DM. Another 721 (17%) AAs and 289 (12%) EAs had incident DM in old age. Following incident DM, cognitive decline increased by 36% among AAs and by 40% among EAs compared to those without DM. No significant difference was observed between AAs and EAs ($p = 0.64$). However, cognitive decline increased by 17% among AAs with preexisting DM compared to those without DM, but no increased decline was observed among EAs with preexisting DM. In secondary analyses, faster decline in executive functioning and episodic memory was observed following incident DM.

Conclusions: In old age, faster cognitive decline was present among AAs and EAs following incident DM, compared to cognitive decline prior to DM, and among those without DM. This underscores the need for stronger prevention and control of DM in old age. *Neurology*® 2016;87:1681-1687

GLOSSARY

AAs = African Americans; **CHAP** = Chicago Health and Aging Project; **CI** = confidence interval; **DM** = diabetes mellitus; **EAs** = European Americans; **HMO** = health maintenance organization; **MMSE** = Mini-Mental State Examination.

Type 2 diabetes mellitus (DM) is associated with poor cognitive performance.¹⁻⁴ Several studies have found preexisting DM to be associated with worsening cognition among older women^{5,6} and among those with higher severity of DM.⁷⁻⁹ This association appears to be stronger among those who develop DM during midlife,¹⁰⁻¹³ particularly among those with a longer duration of DM,¹⁰ and across several areas of cognition including decline in memory^{10,11} and executive functioning.^{10,14} Some studies have reported that incident DM is not associated with worsening cognition, even though these studies found preexisting DM to be associated with cognitive decline.^{9,15} However, the onset of DM during late life is still not well-understood. The association of preexisting and incident DM during late life (over 65 years of age) has not been well-examined. It is in this age group that cognitive decline and DM have their highest prevalence and incidence.

African Americans (AAs) tend to develop DM earlier and have a higher prevalence and incidence of DM than European Americans (EAs).¹⁶⁻¹⁸ A racial difference in the association of DM with poor cognitive function is believed to be mediated by poverty¹⁹ and vascular risk factors.²⁰ No difference in the association of DM with cognition was found in a cross-sectional study,²¹ or in long-term change in cognition following an onset during midlife.¹⁰ AAs had

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faster cognitive decline following preexisting DM than EAs in old age.^{22,23} However, the association of late-life onset of DM with cognitive decline among AAs and EAs is not well-investigated.

Our study examines whether incident and preexisting DM are associated with reduced cognitive function and decline in cognitive function as compared to no DM and whether there are racial differences in a cohort over 65 years of age.

METHODS The Chicago Health and Aging Project (CHAP) is a biracial population-based study of participants from 4 urban Chicago neighborhoods.²⁴ This study started in 1993 by enrolling 79% of all residents over the age of 65, and residents who reached 65 years of age were also enrolled in successive cohorts from 2001. In-home interviews were conducted in approximately 3-year cycles when cognitive function tests were administered.

A flow diagram of the data collection and analytical sample is shown in figure e-1 at Neurology.org. A total of 10,801 participants were enrolled in the CHAP study, of whom 2,195 (20%) had died without a second cognitive assessment, 775 (7%) were only interviewed once due to successive enrollment scheme, 67 (0.6%) never provided a second follow-up assessment, 13 (0.1%) had missing insulin or medication data, and 11 (0.1%) had missing education and were excluded from our study sample.

Cognitive function. Cognitive function was evaluated by a brief battery of 4 tests, including a test of perceptual speed, which is a test of executive function (Symbol Digit Modalities Test),²⁵ 2 tests of episodic memory (immediate and delayed recall of the East Boston Story),^{26,27} and a test of global cognition (the Mini-Mental State Examination [MMSE]).²⁸ Episodic memory test scores were based on the average of the standardized test scores for the 2 recalls, the executive function score was based on the standardized Symbol Digit Modalities Test, and the global cognitive performance was based on a standardized MMSE test score. A composite cognitive performance test score was created by centering and scaling each individual test score to respective baseline mean and SD, and then averaging the 4 tests together. A participant whose composite performance matches the average participant at baseline has a composite score of 0, whereas positive and negative scores were indicators of better and poor cognitive performance, respectively. The reasons for creating a composite cognitive function test score are as follows: (1) the test scores loaded on a single factor account for about 75% of the variance in the composite measure²⁹; (2) a composite measure, which is based on several related individual cognitive tests that vary in difficulty, can accommodate a wider range of performance than the individual tests. As a result, such a composite measure can accommodate errors due to floor and ceiling artifacts; (3) the MMSE is also a measure of global cognition, but its skewed distribution poses analytic challenges, whereas the composite measure of global cognition has an approximately normal distribution.

Standard protocol approvals, registrations, and patient consents. Rush University Medical Center Institutional Review Board approved the CHAP study. At the beginning of the study, written informed consent was obtained from all participants.

Diabetes mellitus. During in-home interviews performed between 1993 and 2012, participants were asked to show all the medications currently being used. Each medication label was recorded and classified, and participants were also inquired specifically about insulin and oral hypoglycemic use. Our participants were aged 65 years or older and were qualified for reimbursement of medical services for physician visits and inpatient and outpatient hospitalization through the Center for Medicare and Medicaid Services. Even if some participants were actively involved in a health maintenance organization (HMO), they would be included our study if they had provided data on insulin medication use. In CHAP, 83% of the participants were enrolled in Medicare and 17% in an HMO, with Medicare claims data complete through December 31, 2010. For this study, we created composite measures of incident and preexisting DM if they used hypoglycemic medication or Medicare services at baseline or anytime during follow-up, which indicated a diagnosis of DM. We collected HbA1c during follow-up period 5 and 6, towards the end of the study. This did not allow us to use HbA1c as the primary measure of interest; however, we were able to compare our DM measure to HbA1c. Our DM diagnosis had a concordance measure of 84% compared to self-reported diabetes, and 82% compared to a single measurement of HbA1c over 6.5%.

Health and demographic covariates. Our analysis adjusted for 2 sets of variables: demographic variables, including age (measured in years and centered at 75), sex (male or female), and education (measured in number of years of schooling completed centered at 12), were included in all models; analyses also included health and lifestyle measures, including body mass index (kg/m^2), and chronic health measures, such as uncontrolled hypertension (defined as blood pressure over 150/90 mm Hg) and stroke (using Medicare hospitalization codes),³⁰ and antihypertensive and lipid-lowering medication use. All covariates were selected based on prior evidence of association with cognition, and were measured at baseline, except for hypertension, stroke, and antihypertensive and statin medication use, which were time-dependent measures. Our primary analyses for the association of incident and preexisting DM and composite cognitive decline were stratified by race, while the secondary analyses for individual tests of cognition adjusted for race as a covariate.

Statistical analysis. Descriptive statistics were computed using means and SDs for continuous variables and percentages for categorical variables for participants with incident and without diabetes, stratified by race. We used a generalized linear model to test the differences in continuous and categorical measures due to race (AAs vs EAs), DM (without vs incident), and an interaction of race with incident DM to examine if race was differentially associated with incident DM. We performed a similar analysis for race and preexisting DM on continuous and categorical measures.

For the change in cognitive function over time, we used a piecewise linear mixed-effects regression model with time of incident diabetes as a change point to study cognitive decline before and after incident DM, and a linear cognitive decline after preexisting DM.³¹ Under this approach, we used a linear change in cognitive function following preexisting DM, and compartmentalized time into 2 components, time before diabetes for those without DM and those with incident DM, and time after incident DM. A comparison of cognitive slopes for those without DM and those before incident DM showed no significant difference; hence, we combined those 2 cognitive slopes into a single coefficient. We included random effects for the intercept and slopes in our regression models. Each model also included fixed

effects for main effects of time before and after incident diabetes, and adjusted for demographic variables and time-dependent health measures. All models were fitted using SAS software.³² Since piecewise mixed models assumed that data were missing at random, participants who died during follow-up might have a differential association on cognitive trajectories. We accounted for cognitive measures not missing at random using a shared parameter model for cognitive decline and time to dropout or mortality,³³ as a sensitivity analysis in R program.³⁴ Given that 20% of participants died without a follow-up interview, we expect these sensitivity models to have greater association on preexisting DM rather than incident DM.

RESULTS Study participants. The study sample consisted of 7,740 participants over the age of 65 years, with data on hypoglycemic medication use or DM inpatient and outpatient physician medical care, and 2 or more cognitive function assessments. On average, participants with DM data had a median of 4 follow-ups over 9.4 years. Of the 7,740 participants, 1,006 (13%) had preexisting DM, and of the remaining 6,734 participants, 1,010 (15%) had incident DM. Among participants with preexisting DM, the length of follow-up was similar between EAs and AAs ($p = 0.25$). The median follow-up time for participants with incident DM before and after the diagnosis was 4.6 and 4.8 years, respectively.

As shown in table 1, the average age at diagnosis of incident DM was not different from the average age of participants with preexisting DM ($p = 0.23$). Participants with preexisting DM had significantly higher BMI, and had higher proportion with stroke and taking antihypertensive and statin medications compared to participants with no DM and incident DM.

A significantly higher percentage of AAs (17%) had incident DM compared to EAs (12%) (table e-1). AAs with incident DM were more likely to be female, with

significantly higher body mass index, compared to EAs with incident DM. No significant differences between the 2 racial groups were observed for other demographic and health characteristics. The differences between AAs and EAs with preexisting DM and without DM were minimal, where a higher number of EAs with antihypertensive and statin users also had preexisting DM (table e-2).

Cognitive decline following incident DM. Both AAs and EAs with incident DM exhibited increased cognitive decline compared to those without DM, as shown in table 2. Among AAs without DM, composite cognitive function declined by a mean of 0.053 units per year. In contrast, cognitive decline increased significantly after incident DM, from 0.053 units per year to 0.072 units per year, roughly 36% faster (95% confidence interval [CI] 30%–42%; $p < 0.001$). Among EAs without DM, composite cognitive function declined by 0.070 units per year; cognitive decline was also substantially higher among EAs after incident DM, from 0.070 units per year to 0.098 units per year, roughly 40% faster (95% CI 31%–49%; $p < 0.001$). The relative contribution of incident DM to the rate of cognitive decline was similar between AAs and EAs ($p = 0.64$). The course of change in cognitive function before and after incident DM in year 5 is shown in figure 1A.

Cognitive decline following preexisting DM. Table 2 also shows the results for preexisting DM. Cognitive decline was moderately faster among AAs with preexisting DM, 0.062 unit per year, about 17% faster (95% CI 10%–24%; $p = 0.034$) than those without DM. Cognitive decline among EAs with preexisting DM was not different from those without DM ($p = 0.75$).

Table 1 Sample characteristics of 7,740 study participants stratified by diabetes mellitus (DM) status

	No DM (n = 5,724), mean (SD) or n (%)	Preexisting DM (n = 1,006), mean (SD) or n (%)	Incident DM (n = 1,010), mean (SD) or n (%)	No vs preexisting, p value	No vs incident, p value	Preexisting vs incident, p value
Age at diagnosis, y	72.5 (6.5)	71.7 (5.7)	71.5 (5.6)	0.0002	<0.0001	0.23
Education, y	12.6 (3.6)	11.8 (3.2)	12.1 (3.7)	<0.0001	0.0002	0.071
Body mass index, kg/m ²	27.6 (5.7)	30.1 (6.3)	29.3 (6.0)	<0.0001	<0.0001	0.005
Composite cognition ^a	0.304 (0.731)	0.204 (0.724)	0.224 (0.693)	<0.0001	0.001	0.53
Executive function	0.388 (0.942)	0.184 (0.884)	0.267 (0.921)	<0.0001	0.0001	0.044
Episodic memory	0.299 (0.839)	0.247 (0.860)	0.212 (0.815)	0.078	0.002	0.34
MMSE	0.278 (0.686)	0.189 (0.683)	0.237 (0.660)	<0.0001	0.005	0.004
Female, %	3,624 (63)	617 (61)	604 (60)	0.23	0.033	0.48
Hypertension, %	1,392 (24)	262 (26)	252 (25)	0.24	0.67	0.57
Stroke, %	432 (8)	124 (12)	88 (9)	<0.0001	0.20	0.008
Antihypertensive medication, %	3,146 (55)	787 (78)	648 (64)	<0.0001	<0.0001	<0.0001
Statin medication, %	784 (14)	203 (20)	139 (14)	<0.0001	0.96	0.001

^a See text for description; based on tests of executive function, episodic memory, and the Mini-Mental State Examination (MMSE).

Table 2 Annual change in composite cognitive function and difference in the level of composite cognitive function among African Americans (AAs) and European Americans (EAs) with and without incident or preexisting diabetes mellitus (DM)

	Coefficient (SE, <i>p</i>) ^a	
	AAs	EAs
Annual change in cognitive function		
Incident DM	−0.072 (0.006, <0.001)	−0.098 (0.009, <0.001)
Preexisting DM	−0.062 (0.004, <0.001)	−0.071 (0.008, <0.001)
Without DM	−0.053 (0.003, <0.001)	−0.070 (0.003, <0.001)
Difference in level of cognitive function		
Incident DM	−0.035 (0.021, 0.105)	−0.034 (0.032, 0.281)
Preexisting DM	−0.050 (0.024, 0.037)	−0.007 (0.035, 0.84)
Without DM	Referent	Referent

^a Adjusted for baseline age, sex, education, body mass index, and time-dependent hypertension, stroke, and antihypertensive and statin medication use.

However, including a race-interaction term suggests that AAs did not have faster cognitive decline following preexisting DM than EAs ($p = 0.066$). Figure 1B shows the change in cognitive function for participants with preexisting DM.

Using our regression models, we also found that participants with incident DM had increased cognitive decline vs participants with preexisting DM among both AAs ($p = 0.028$) and EAs (0.001).

Baseline level of cognitive function. From the regression models (table 2), after adjusting for demographic and

health measures, participants with incident DM had baseline level of cognitive function similar to those without DM among AAs and EAs. However, the baseline level of cognitive function was significantly lower by 0.050 unit among AAs with preexisting DM, but not among EAs, compared to those with no DM.

We performed a sensitivity analysis for truncation due to mortality, since our mortality rate was higher than our dropout rate (table e-3). We found that the estimates of cognitive decline following preexisting and incident DM increased slightly among AAs

Figure 1 Course of change in composite cognitive function for a participant with incident diabetes mellitus (DM) at fifth year of observation and preexisting DM among African Americans (AAs) and European Americans (EAs)

Red line shows cognitive decline among EAs and blue line shows cognitive decline among AAs. Dashed line shows cognitive decline among those with incident DM (A) and preexisting DM (B), while solid line shows cognitive decline among those without DM in both panels.

and EAs, perhaps suggesting that mortality did not attenuate our estimates drastically. Preexisting DM was still not associated with faster cognitive decline among EAs. Adding a quadratic term for age, smoking behaviors, and amount of alcohol consumption did not change our estimates of cognitive decline following incident or preexisting DM (data not shown). After excluding participants with stroke, the difference in baseline level of cognitive function between participants with preexisting DM and participants without DM was no longer significant (table e-4). However, our estimate of cognitive decline following preexisting DM and incident DM did not change.

Individual cognitive tests following preexisting and incident DM. Because cognitive decline is not a unitary process and may differentially affect different cognitive domains, we next examined the association of incident and preexisting DM with individual tests of cognition. We combined the data from both races for these analyses, since we found no significant difference between AAs and EAs in the association of incident DM with composite cognitive function. As shown in table 3, decline in executive function increased by 0.017 unit per year (SE 0.004; $p < 0.001$), in episodic memory by 0.011 unit per year (SE 0.005; $p = 0.017$), and in the MMSE by 0.034 unit per year (SE 0.005; $p < 0.001$). Preexisting DM was associated with faster decline in executive function by 0.007 unit per year ($p = 0.036$). Participants with incident DM had baseline level of individual tests similar to those without DM. However, participants with preexisting DM had significantly lower executive function and MMSE score than participants with no DM.

DISCUSSION In this population-based, longitudinal cohort study, we found that incident DM in old age

was associated with faster decline in composite cognitive function than preexisting DM. We also found that AAs had more incident and more preexisting DM than EAs. The finding of increased cognitive decline following incident DM was observed among AAs and EAs, by similar rates. Cognitive decline was also faster among AAs with preexisting DM than those without DM, while this association was not observed among EAs.

Current studies of the association of onset DM in old age with cognitive decline suggest no association.^{9,15} The incidence of DM was twice as high as in previous studies,⁹ but our sample was also twice as large, and had twice the length of follow-up. Furthermore, our participants without DM had similar rates of decline as participants prior to incident DM, suggesting that the incident DM cases in our study did not develop DM after cognitive impairment.

Several studies have examined the association of DM and cognitive decline in old age⁷⁻⁹ and in midlife.¹⁰⁻¹³ The long-term association of midlife DM with cognitive decline appeared stronger than late-life DM with no difference in the association between AAs and EAs.¹⁰ Even though we found no racial difference in the association of preexisting DM with cognitive decline between AAs and EAs, we found this association only among AAs. This suggests that preexisting DM needs to be better controlled and managed among AAs, who seem to have more adverse cognitive deficits than their EA counterparts.

Because cognition is not a unitary process and because identifying potential differential associations on cognition may lead to clues about pathophysiologic mechanisms, we also examined the association of incident and preexisting DM to individual tests of cognition, which represent different cognitive systems.

Table 3 Annual change and difference in level of individual tests of executive function (EF), episodic memory (EM), and the Mini-Mental State Examination (MMSE) among persons with and without preexisting or incident diabetes mellitus (DM)

	Coefficient (SE, p) ^a		
	Executive function	Episodic memory	MMSE
Annual change in individual tests of cognition			
Incident DM	-0.078 (0.004, <0.001)	-0.050 (0.005, <0.001)	-0.107 (0.003, <0.001)
Preexisting DM	-0.068 (0.003, <0.001)	-0.040 (0.004, <0.001)	-0.080 (0.004, <0.001)
Without DM	-0.061 (0.002, <0.001)	-0.039 (0.003, <0.001)	-0.073 (0.003, <0.001)
Difference in level of individual tests of cognition			
Incident DM	-0.036 (0.018, 0.051)	-0.035 (0.021, 0.105)	-0.035 (0.032, 0.281)
Preexisting DM	-0.071 (0.023, 0.002)	-0.009 (0.025, 0.71)	-0.049 (0.020, 0.015)
Without DM	Referent	Referent	Referent

^a Adjusted for baseline age, race, sex, education, and time-dependent hypertension, stroke, and antihypertensive and statin medication use.

Executive function and episodic memory, as well as the MMSE, showed significantly increased cognitive decline following incident DM, compared to those without DM. Earlier studies did not find an association of incident DM with faster cognitive decline in the executive function or the MMSE⁹ and memory scores.¹⁵ Preexisting DM in old age was associated with faster decline in executive function¹⁴ but not memory scores or MMSE, a finding consistent with a previous study.¹⁰ Since AAs might have longer duration and more severe preexisting DM, the burden of preexisting DM might lead to worsening in executive functioning, but not on other tests of cognition.

Some limitations of this study need to be noted. Our study does not allow us to make inferences on short-term cognitive decline, since follow-up interviews were approximately 3 years apart. The selection of individuals for this study was restricted to those who had survived at least 6 years since baseline assessment. However, our sensitivity analysis for mortality suggests that our estimates may be conservative. Our study collected data on executive functioning, episodic memory, and the MMSE, but not other tests of cognition. The creation of a composite DM measure by combining oral hypoglycemic medication use and inpatient and outpatient electronic medical records to assess incident and preexisting DM have both advantages and disadvantages. The advantage is that DM has advanced to glucose levels requiring physician treatment, and the disadvantage is that it excludes people with mild glucose disorders, who have not yet been treated. There are studies that show cognition to go down with insulin resistance and metabolic syndrome without glucose elevation that often precedes DM.³⁵ Even though our findings were based on more severe DM, they also seem to be consistent with mild glucose disorders. Our study did not adjust for glomerular filtration rate, since it was only available in about 24% of participants prior to incident DM. More research is needed to see whether this association may be graded.

Incident DM was associated with faster rate of future cognitive decline, which seems to be similar among AAs and EAs. Therefore, preventing and controlling onset of DM in old age might also prove beneficial in reducing future cognitive decline among AAs and EAs.

AUTHOR CONTRIBUTIONS

Dr. Rajan designed and conceptualized the study, conducted data analysis, interpreted the findings, and drafted and revised this manuscript. Drs. Arvanitakis, McAninch, and Lynch provided critical revision of this manuscript for intellectual content. Drs. Wilson, Weuve, Barnes, and Bianco reviewed and revised this manuscript for intellectual content. Dr. Evans acquired the study data and provided critical revision of this manuscript for intellectual content.

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