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Diabetes and cognitive decline in elderly African Americans: a 15 year follow up study

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Abstract

Background—Diabetes mellitus is associated with increased risk of cognitive impairment and vascular factors appear to play a role in this relationship. In a sample of elderly African Americans, with a follow up duration of 15 years, we tested the hypothesis that diabetes accelerates cognitive decline and explored possible mediating mechanisms.

Methods—A total of 1702 subjects, of which 441 had diabetes, were given the Community Screening Interview for Dementia (CSI-D) to measure cognitive functioning at 6 time points, over 15 years. Mixed effects models with repeated measures were used to examine the association of diabetes, and vascular risk factors with cognitive scores over time.

Results—African Americans with diabetes were shown to have significantly accelerated cognitive decline compared with those without diabetes ($p=0.046$) when controlling for basic demographics and baseline co morbid conditions (heart disease, hypertension, stroke and depression). Adjusting for incident heart disease, and especially stroke weakened this association ($p=0.098$) indicating a mediating effect of stroke on the association of diabetes and cognitive decline. However when incident stroke is incorporated into the model, the effect for participants with diabetes is greatly increased ($p=0.007$)

Conclusions—Diabetes, mediated by cerebrovascular pathology, accelerates cognitive decline in an African American sample with a follow up duration of 15 years.

Keywords

diabetes; cognitive decline; cerebrovascular disease; longitudinal study; elderly African American

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Introduction

Compelling evidence from cross-sectional and longitudinal studies support the view that people with diabetes are at increased risk of developing cognitive impairment (1) and dementia (2). Cognitive functions primarily affected are complex attention tasks, mental flexibility, speed of information processing and verbal memory. A recent study for example demonstrated that middle-aged persons with type 2 diabetes showed a greater decline in cognitive function than middle-aged persons without diabetes after adjustment of demographic factors (3). Another study, which included elderly participants, also found that people with diabetes had significantly lower baseline scores and lower cognitive scores during follow-up (4). Cognitive dysfunction in diabetes may result from an interaction between metabolic abnormalities such as hyperglycemia; diabetes complications such as retinopathy and neuropathy; and other diabetes-related disorders such as ischemic heart disease, cerebrovascular disease, hypertension, central obesity, and depression. It is not clear however, what the contribution of these factors is in the association between diabetes and cognitive decline.

The prevalence and incidence of type 2 diabetes appears to be higher in African-Americans than in Caucasians (5) and African-Americans are also at increased risk for complications as a result of diabetes (6), including cognitive decline (7).

Since 1992, research teams from Indiana University (Indianapolis) and the University of Ibadan (Ibadan, Nigeria) have been collaborating to study the rates and risk factors for age-associated dementia and AD in elderly African Americans and Yoruba. Because this study has a long follow up duration (15 years), included African American subjects, who are susceptible for the development of diabetes and its complications and in whom the relation between diabetes and cognition is understudied, it gives us the unique opportunity to have a closer look at vascular risk factors and their potential contribution to cognitive decline in this population. In this analysis we will test the hypothesis that diabetes accelerates cognitive decline and we explore possible mediating mechanisms that potentially underlie this association.

1. Methods

2.1 Population

The Indianapolis Ibadan Dementia Project is an ongoing prospective community-based comparative epidemiologic study of rates and risk factors for age-associated dementia and Alzheimer's disease (AD) in African Americans living in Indianapolis and Yoruba Nigerians. In this study, we focused on the African American Indianapolis cohort of the Indianapolis-Ibadan Dementia Project.

In 1992, a random sample of 2,212 African Americans age ≥ 65 years was assembled. The target geographic sampling frame for the study was 29 contiguous census tracts within Indianapolis, Indiana, USA. According to the 1990 US Census, 80% of the population within these census tracts was African-American representing two-thirds of all elderly African-Americans living within the city. The sample was representative of elderly African-Americans throughout Indianapolis and Indiana in its age, gender, and socioeconomic composition. Interviewers who were members of the targeted community canvassed the neighborhoods and with randomized address lists identified homes to interview African-American subjects ≥ 65 years of age. When possible, a close relative within the subject's household participated in the interview as an informant to provide, verify, or supplement data.

Of the 7,590 residential addresses provided, 4,915 households were ineligible because none of the members of the household were 65 years of age or older and 383 households had no African-Americans family members. Of the 2,582 eligible subjects, 249 (9.6%) refused participation and 121 (4.7%) were too ill to participate. A total of 2,212 subjects completed the baseline in-home interviews and 1,495 (67.6%) of these subjects had accompanying informants during their interviews. Details of the construction of the original sample have been previously reported (8). The 1992 evaluation constitute study baseline for participants in this cohort. Written informed consent was obtained from study participants and the study was approved by the Institutional Review Board of Indiana University.

2.2 Research Design

Participants in this cohort were evaluated at baseline and five follow-up evaluations during 15 years from 1992 to 2007. The baseline wave of the study was conducted from 1992 to 1993. The next wave was conducted 2 years later from 1994 to 1995 and the third wave was conducted approximately 5 years after the original from 1997 to 1998. The remaining 3 waves were conducted in 2001, 2004, and 2007. During each evaluation, participants were given the Community Screening Interview for Dementia (CSI-D) as part of a home visit. The CSI-D assesses the subject's cognitive status and collects both demographic and medical history information. Both Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) (9) and International Classification of Diseases, 10th Revision (ICD-10) (10) criteria were used to diagnose dementia and to rate dementia severity. Participants had to satisfy both sets of criteria to be counted as having dementia. There were no participants who satisfied ICD-10 criteria who did not also satisfy DSM-III-R criteria. The National Institute for Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association criteria (11) were used for probable and possible AD; ICD-10 criteria were used for vascular dementia and other secondary dementias. Details of the research design were previously published (12).

2.3 Cognitive Assessment

The Community Screening Interview for Dementia (CSI-D) was previously used in comparative epidemiological studies of dementia in culturally disparate, nonliterate and literate populations (10). The instrument has demonstrated good inter-rater reliability (99.4%), sensitivity specificity levels (0.82-0.97 depending on the site) as well as good validity in detecting dementia in various populations (13-14). The cognitive test was conducted during a home visit by a physician or specially trained research nurse. The cognitive assessment included items to test the following cognitive domains: language (naming, definition, fluency, and comprehension–motor response), attention and calculation, memory (short term and long term), orientation (time, place), and praxis– copying. Included in the CSI-D total scores are delayed recall of the East Boston Story, number of animals recalled in 60 seconds (capped at a maximum of raw score of 23 (95th percentile). The CSI-D scoring is a single test with 42 separate items and a cognitive score range of 0-80, with higher scores indicating better cognitive functioning. The same cognitive test was given at each evaluation to all subjects.

2.4 Collection of Other Information

In addition to the cognitive assessment, the screening process included basic demographic information about the subject including age, gender and education, family history of dementia, medical history from both the subject and a relative of the subject if possible, smoking and regular alcohol use. Medical history included diabetes, depression, cancer, hypertension, stroke, Parkinson's disease, heart disease, and head injury. Ascertainment of a medical condition was confirmed with either the subject or the relative report. At the time each cognitive assessment was scheduled, the participant was told that the interviewer would

need to see all of the medications he or she was currently taking. During the home visit the interviewer recorded the name of the medications from the labels on the bottles, or from a printed list participants obtained from their physicians (15-16). Medications were classified into pharmacologic classes, including anti-hypertensive and anti-diabetic medications. Information on medical conditions and medication use were collected at baseline and at each follow-up evaluation.

In this study, diabetes diagnosis was ascertained based on either self or informant report or on the use of anti-diabetic medications. Hypertension was defined as self or relative report or the use of antihypertensive medications. Diabetes diagnosed by self-report has been used in large cohort studies previously (3-4) and studies conducted to validate self-reported diabetes demonstrated high accuracy of self-report for diabetes (17-18). In the analyses, we distinguished between medical conditions ascertained at baseline and those obtained during follow-up evaluations.

2.5 Statistical analyses

Demographic and baseline characteristics of subjects with and without diabetes at baseline were compared using *t*-tests for continuous measures and chi-square tests for categorical measures. Chi-square tests were also used to compare post-baseline cardiovascular conditions (heart disease, hypertension and stroke) between subjects with and without diabetes at baseline.

A series of mixed effects models with repeated measures were used to examine the association of diabetes, other medical conditions and demographic characteristics with cognitive scores over time. All models included baseline diabetes as the independent variable of interest, time (years since baseline) and a term for the interaction between diabetes and time while adjusting for different sets of covariates by including all covariates as main effects and interaction terms between each covariate and time. Parameter estimates for the main effects reflect difference in cognitive scores at baseline between subjects with diabetes and those without. Parameter estimates for the interaction term (slope) estimates the difference in average annual change in cognitive scores between subjects with diabetes and those without. To examine whether the association between diabetes and cognitive decline was mediated by cardiovascular conditions acquired after baseline, we created time-dependent covariates for heart disease, hypertension and stroke identified during follow-up evaluations and added those variables to the mixed effect models. In addition, we conducted stratified analyses examining the effect of diabetes in three groups: a group of subjects without stroke, a group with baseline stroke, and a group with incident stroke defined as stroke reported after baseline.

3 Results

A total of 2212 subjects were enrolled and evaluated at baseline. We excluded 13 subjects with missing cognitive information, 65 subjects who were diagnosed with dementia and 22 subjects with missing covariate information. In addition, 408 subjects had no follow-up evaluation and were also excluded. Thus, 1702 subjects were included in the analyses. Of these, 441 (25.9%) subjects had diabetes at baseline of which 265 (60.1%) were taking medications, either insulin or sulfonylurea's (metformin wasn't approved by the FDA in 1992 when this study started).

Overall, the length of follow-up ranged from 0.9-15.2 years with a median of 4.9 years and a mean of 6.7 years. A total of 264 (15.5%) completed the 15 year evaluation, 192 (11.3%) completed the 12 year evaluation, 274 (16.1%) were followed for 9 years, 500 (29.4%) were followed for 5 years, and 472 (27.7%) were followed for 2 years. There was no difference in

mean length of follow-up between subjects with and without diabetes (6.4 vs. 6.8 years; $p=0.143$). However, within the diabetes group, 283 subjects (64.2%) died at some point during follow-up compared to 646 (51.2%) in the non-diabetes group ($p<0.0001$). Mean cognitive scores at the six time points were 67.0 ($n=1702$, standard deviation (SD) =7.6) at baseline, 67.5 ($n=1635$, SD=7.3) at 2-year, 63.8 ($n=1218$, SD=9.0) at 5-year, 63.9 ($n=714$, SD=10.2) at 9 years, 64.8 ($n=455$, SD=9.0) at 12-year and 66.9 ($n=264$, SD=9.1) at 15-year follow-up evaluations.

Participant's baseline characteristics, stratified by diabetic status, are shown in Table 1. Participants with diabetes were more likely to be female, and significantly younger compared to those without diabetes. Furthermore, they had a higher rate of reported family history of dementia, more depression, heart disease, hypertension and stroke. No differences were noted between the two groups in education, baseline cognitive score, history of cancer, alcohol use, head injury, smoking and Parkinson's disease. People who dropped out of the study prior to the last follow-up due to death had lower baseline cognitive scores than those who finished or dropped out due to other reasons (cognitive score: 66.5 ± 7.5 vs 67.6 ± 7.6 ; $p=0.003$)

The group with diabetes at baseline had a significantly higher rate of post-baseline stroke identified during follow-up than those without diabetes (13.5% vs. 9.2% ($p=0.017$)). Also, a higher post-baseline hypertension rate was observed in those with baseline diabetes (55.2% vs. 42.2%, $p=0.029$). The rate of post-baseline heart disease did not differ between the two groups.

Results of the mixed effects models examining the association between baseline diabetes and cognitive change over time are presented in Table 2. When controlling for basic demographics and baseline co morbid conditions (heart disease, hypertension, stroke and depression) in the model (model 1), subjects with diabetes were shown to have significantly more decline of cognitive scores than those without diabetes ($p=0.046$). Figure 1 shows the estimated cognitive trajectories representing annual change in cognitive scores in the diabetic and non-diabetic subjects based on model 1. On average, those with diabetes at baseline declined 0.10 point more per year than those without diabetes, while a one year increase in age results in a decline of 0.04 points more per year in the same model. Hence the effect of diabetes at baseline on cognitive decline is equivalent to being 2.5 years older in age. While baseline stroke was significantly associated with lower cognitive score at baseline ($p=0.003$), it was not associated with cognitive decline observed during follow-up ($p=0.299$).

Models 2 and 3 were used to examine any potential mediating effect of incident cardiovascular conditions on the association between diabetes and cognitive decline. While adjusting for post-baseline hypertension increased the strength of association between diabetes and cognitive decline ($p=0.030$), adjusting for post baseline heart disease, and especially stroke weakened the association seen in model 1 and diabetes was no longer significant for cognitive decline (0.098) indicating a mediating effect of stroke on the association of diabetes and cognitive decline.

If stroke is indeed the factor mediating the association between diabetes and cognitive decline, diabetes and cognitive decline would be unrelated in the majority of the population, i.e., in those without stroke. We present results of stratified analyses examining the effect of diabetes in three groups of subjects defined by stroke status in Table 3. Diabetes was not associated with cognitive decline in either the group without any stroke ($p=0.267$) or the group with baseline stroke ($p=0.327$). However, diabetes was significantly associated with cognitive decline in the group experiencing incident stroke ($p=0.007$), i.e. stroke occurred

after the baseline evaluation. On average, those with diabetes at baseline declined 0.40 point more per year than those without diabetes, as compared to a 0.02 point decline for each one year increment in age in the same model. Hence the effect of diabetes at baseline on cognitive decline is equivalent to the effect of being 20 years older.

4 Discussion

The results of our study indicate that over a 15 year period, in an African American elderly population, after adjusting for demographics and co morbid conditions, participants with diabetes had a modest but significant increase in cognitive decline than did their non diabetic peers. This increase in cognitive decline is equivalent to that of a 2.5 year increase in age. The analysis also supports the hypothesis that the effect of diabetes on cognitive decline is mediated at least in part by the influence of diabetes related vascular conditions and in particular with stroke. When incident stroke is incorporated into the model, the risk for participants with diabetes is greatly increased ($p=0.007$), approximately equivalent to 20 year increase in age.

Stroke has been associated with poor cognitive outcomes in previous studies. One study reported an increase risk of Alzheimer Disease in individuals with a history of stroke (19). This risk was highest for those with stroke who also had established vascular risk factors, such as high blood pressure, type 2 diabetes, or heart disease. Supporting these findings are the results of a recent systematic review of cardiovascular risk factors and incident AD, concluding that evidence for a significant association between single cardiovascular risk factors (such as hypertension and diabetes) and incident AD is mostly negative, but interactions between these risk factors were found to have some modifying risk for AD (20). For example, a study exploring the association of the aggregation of vascular risk factors with AD found that the risk of AD increased with the number of vascular risk factors. Diabetes and current smoking were found to be the strongest risk factors, but clusters including hypertension and heart disease also increased the risk of AD (21).

Results of our study also point to interactive effects of risk factors on cognitive decline: people with both diabetes and cerebrovascular disease were at greater risk for cognitive decline than people with diabetes alone. Consideration of interactions therefore should play a significant role in identifying a vulnerable population and treatment strategies with a multi-factorial approach seem appropriate.

Our observation that diabetes was significantly associated with cognitive decline in the group experiencing incident stroke but not in the group with prevalent stroke can probably be attributed to the fact that participants with prevalent stroke include long term survivors who have sufficient time to recover from the effect of the stroke, while those experiencing incident strokes still demonstrate more acute effect of stroke on cognitive function. Several studies have reported that cognitive impairment after stroke may improve over time (22-25). Unfortunately our research design did not allow us to evaluate this effect directly in our study.

Our findings that incident hypertension did not appear to mediate the effects of diabetes on cognitive decline can probably be attributed to the high prevalence of hypertension at baseline (80%) in the participants with diabetes. Reports on the effects of hypertension occurring in late life (as our incident cases) and cognitive decline have been inconsistent (26).

There are a number of limitations to our study which need to be acknowledged. The effect of diabetes on cognitive decline in our analysis was modest. With our cognitive instrument it was difficult to distinguish effects on separate cognitive sub domains. Furthermore, a

number of potentially important diabetes related variables such as dislipidaemia and body mass index were not included. All these variables might have an additional or synergetic effect on our outcome. The diagnosis of diabetes relied on self or informant report or use of medication. Blood glucose levels were not available. As diabetes is commonly undiagnosed, a proportion of people with diabetes might have been erroneously assigned to the non-diabetic group thus diluting the results (underestimating the association between diabetes and cognitive decline).

We were not able to distinguish between type 1 and type 2 diabetes, but given the age of the population and the treatment regime it is likely that the vast majority of the participants had type 2 diabetes.

An important limitation in all longitudinal studies is the vulnerability to survivor bias. Individuals who completed the longitudinal assessments comprised the healthier subset of the original cohort or are relatively less susceptible to the adverse effects of present risk factors. Because of loss of follow up of subjects with more disease burden and cognitive impairment and because of death, we might have underestimated the degree of cognitive decline and the effect of its determinants over the 15 years of follow-up. We partially accounted for loss of follow up by applying mixed effects models, which use all available data during follow up. Thus for many subjects who died during the study, their repeated cognitive measures at evaluations prior to death were included in our analyses. Nevertheless, mixed effects models rely on a crucial assumption that loss to follow-up was random given the variables included in the models. Although we included many co morbid conditions (cancer, heart disease, stroke, hypertension and diabetes) that contribute to increased mortality in the elderly, it is possible that conditions not collected in the study can influence loss to follow-up and therefore threatening the validity of the models used in our investigation. Furthermore, our study included only African Americans so caution should be used before extrapolating these findings to other groups.

Strengths of the study are its long follow up duration, large sample size and the inclusion of a population comprising African Americans, who are at greater risk for diabetes but in whom the relation between diabetes and cognition is understudied. Furthermore, because vascular risk factors were included in the models, we were able to study the effect of these factors as mediators.

In this study we showed that diabetes, mediated by stroke, accelerates cognitive decline in an African American sample with a follow up duration of 15 years, thus emphasizing the need for stroke prevention strategies in patients with diabetes (27).

Future studies that included more sophisticated cognitive measurement instruments and more detailed diabetes related information and in particular information on treatment strategies may provide more insight into the relationship between diabetes and cognition and possibly suggest best prevention strategies for future clinical trials.

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Abbreviations

AD	Alzheimer's disease
CSI-D	Community Screening Interview for Dementia

DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition
ICD-10	International Classification of Diseases, 10th Revision
SD	standard deviation

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Figure 1.

Estimated cognitive trajectories representing annual change in cognitive scores for subjects with (solid line) and without diabetes (dashed line)*

* Trajectories of cognitive decline over time for the subjects with and without diabetes come from a mixed effects model with repeated measures on cognitive scores over time adjusted for years since baseline, age, gender, education, family history of dementia, baseline heart disease, hypertension, stroke, depression and interactions between all with years since baseline.

Table 1

Descriptive baseline characteristics of participants by diabetes status

	Subjects without diabetes (n=1261)	Subjects with diabetes (n=441)	p-value
Female, n (%)	824 (65.3%)	311 (70.5%)	0.047
Age, mean $\pm$ SD	74.2 $\pm$ 6.9	72.8 $\pm$ 6.1	<0.0001
Years of education, mean $\pm$ SD	9.8 $\pm$ 3.0	9.9 $\pm$ 3.1	0.85
Cognitive score, mean $\pm$ SD	67.1 $\pm$ 7.7	66.9 $\pm$ 7.7	0.63
Family history of dementia, n (%)	144 (11.4%)	69 (15.6%)	0.02
Alcohol use, n (%)	497 (39.4%)	187 (42.4%)	0.27
Smoking, ever, n (%)	819 (64.9%)	272 (61.7%)	0.22
History of Cancer, n (%)	132 (10.5%)	55 (12.5%)	0.25
History of Head injury, n (%)	120 (9.5%)	39 (8.9%)	0.68
History of Parkinson's disease, n (%)	11 (0.9%)	5 (1.1%)	0.62
History of Depression, n (%)	76 (6.0%)	61 (13.8%)	<0.0001
History of Heart disease, n (%)	310 (24.6%)	160 (36.3%)	<0.0001
History of Hypertension, n (%)	818 (64.9%)	354 (80.3%)	<0.0001
History of Stroke , n (%)	121 (9.6%)	64 (14.5%)	0.004

Table 2
The association of diabetes with cognitive decline after adjusting for various covariates

	Main Effect			Slope	
	Parameter Estimate	Standard Error	p-value	Parameter Estimate	p-value
Model 1: adjusting for demographics and baseline co morbid conditions*	-0.193	0.378	0.611	-0.099	0.050
Model 2a: Model 1 + heart disease after baseline	-0.206	0.379	0.587	-0.094	0.049
Model 2b: Model 1 + hypertension after baseline	-0.174	0.379	0.647	-0.107	0.050
Model 2c: Model 1 + stroke after baseline	-0.204	0.379	0.590	-0.082	0.049
Model 3: Model 1 + heart disease, hypertension and stroke after baseline	-0.200	0.378	0.595	-0.085	0.049

The results are from mixed effect models including years since baseline, diabetes, and an interaction between the two along with other covariates as indicated. When covariates are listed, they are included both as main effects and as interactions with years since baseline. Parameter estimates for the main effects reflect the differences in cognitive scores at baseline between those with diabetes and those without, and parameter estimates for the slope reflect the differences in annual changes in cognitive scores between those two groups of participants.

* Model 1: adjusting for age, gender, education, family history of dementia, baseline heart disease, hypertension, stroke and depression

The association of diabetes with cognitive decline after adjusting for various covariates and stratifying by baseline and incidence stroke status

Table 3

	Main Effect			Slope		
	Parameter Estimate	Standard Error	p-value	Parameter Estimate	Standard Error	p-value
Subjects without any stroke (n=1361)	-0.111	0.429	0.797	-0.062	0.057	0.267
Subjects with baseline stroke (n=185)	-1.013	1.207	0.402	0.165	0.169	0.328
Subjects with incident stroke (n=156)	-0.118	1.130	0.917	-0.395	0.146	0.007

The results are from mixed effect models including years since baseline, diabetes, and an interaction between the two and also adjusts for baseline covariates including age, gender, education, family history of dementia, heart disease, hypertension, depression, and both heart disease and hypertension after baseline. When covariates are listed, they are included both as main effects and as interactions with years since baseline. Parameter estimates for the main effects reflect the differences in cognitive scores at baseline between those with diabetes and those without, and parameter estimates for the slope reflect the differences in annual changes in cognitive scores between those two groups of participants.