Cognitive Decline in Older Mexican Americans with Diabetes

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Financial support: This study was supported by grants AG10939, AG17638 and P60AG17231 from the National Institute on Aging (United States), and in part by the UTMB Center for Population Health and Health Disparities (1P50CA105631). Dr. Al Snih was supported by a fellowship from the National Institute on Disability and Rehabilitation Research (H133P040003). Dr. Raji's work is supported by the Bureau of Health Professions' Geriatric Academic Career Award 1 K01 HP 00034-01.

Preliminary results of the study were presented as a poster at the 2005 annual meeting of the American Geriatrics Society in Orlando, FL.

Objective: To examine social, demographic and health factors associated with cognitive decline over a seven-year period among older Mexican Americans with diabetes.

Methods: A population-based sample of 808 noninstitutionalized Mexican Americans aged ≥65 years with diabetes who had a Mini-Mental State Examination (MMSE) >17 at baseline from the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE). Measurements included sociodemographics, diabetic treatment received (oral hypoglycemic or insulin), self-reported medical conditions, self-reported diabetes-related complications, high depressive symptoms and ADL limitations.

Results: The mean MMSE score at baseline was 25.3 ± (SD=3.7). The rate of decline in cognitive function (MMSE) during the follow-up period was 0.37 point per year. Using general linear mixed models, we found that being male, and having high depressive symptoms and diabetic complications (kidney impairment, circulation problems or limb amputation) were factors significantly associated with greater declines in MMSE score over time.

Conclusion: Circulation problems, kidney impairment and depression are the major factors associated with cognitive decline in older Mexican Americans with diabetes.

Key words: diabetes ■ cognitive decline ■ elderly health ■ Mexican Americans

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INTRODUCTION

Diabetes was diagnosed in 7.8 million people in United States in 1993 and by the year 2003 the number increased to 13.8 million.[1] The overall prevalence of diabetes in 2003 was 17.3% among persons aged ≥65 years old and 15.1% among persons aged ≥75 years old.[1] However, the prevalence varies by ethnicity and gender. Among subjects ≥75 years, 26.9% of Hispanic men and 21.4% of Hispanic women were diagnosed with diabetes. Similarly, 20.8% of black men, 20.3% of black women, 17% of white men and 13.0% of white women were diagnosed with diabetes.[1] The number of Americans diagnosed with diabetes is projected to increase 165%, from 11 million in 2000 to 29 million in 2050, and the largest percent of increase will be among those aged ≥75 years.[2]

The older Hispanic population is projected to grow faster than other groups from just over 2 million in 2003 to 7.6 million by the year 2030, and 15 million in 2050.[2-4] The burden of diabetes is greatest in this population.[4] The burden arises in part from diabetes complications, such as peripheral vascular disease, kidney impairment, depression, heart attack, stroke, vision impairment, neuropathy and cognitive impairment.[5]

Cognitive impairments—mild or severe—and diabetes are associated with increased risk of disability and nursing home placement.[6-7] Several studies have found accelerated cognitive decline and increased incidence of dementia among subjects with diabetes in comparison to subjects without diabetes.[8-10] Leibson and colleagues[9] found that the risk of cognitive impairment among subjects with diabetes differs by gender. Men with diabetes were twice as likely to develop Alzheimer's disease as men without diabetes. Women also experienced elevated risk, but it was not statistically significant. Elias and colleagues[10] found that hypertensive subjects with diabetes are at greatest risk for poor performance on tests measuring visual organization and memory and that subjects treated with diabetes insulin have poorer cognitive performance than those on oral hypoglycemics or diet.

Table 1. Baseline characteristics and mean ± standard deviation of MMSE score for older Mexican Americans with diabetes

Explanatory Variables	N (%)	MMSE Score, Mean ± SD
Overall	808 (100)	24.9 ± 3.8
Age, Mean ± SD	72.5 ± 5.8	
<75	558 (69.1)	25.4 ± 3.6
≥75	250 (30.9)	23.8 ± 3.8
Gender		
Female	485 (60.0)	24.6 ± 3.8
Male	323 (40.0)	25.3 ± 3.6
Education (Years) *		
<8	618 (76.9)	24.2 ± 3.7
≥8	186 (23.1)	27.1 ± 3.2
Marital Status		
Married	472 (58.4)	25.4 ± 3.6
Unmarried	336 (41.6)	24.1 ± 3.8
Medical Conditions		
Hypertension		
Yes	580 (71.8)	24.7 ± 3.7
No	228 (28.2)	25.4 ± 3.8
Stroke		
Yes	65 (8.0)	24.3 ± 4.1
No	743 (92.0)	24.9 ± 3.7
Heart Attack		
Yes	112 (13.9)	25.0 ± 3.9
No	694 (86.1)	24.9 ± 3.7
Depression (CES-D)		
≥16	196 (24.4)	24.3 ± 3.6
<16	608 (75.6)	25.1 ± 3.8
Obesity (BMI)		
≥30 Kg/m^2	299 (39.2)	25.0 ± 3.7
<30 Kg/m^2	464 (60.8)	24.9 ± 3.7
ADL Limitations		
≥1	117 (14.5)	23.7 ± 3.9
None	691 (85.5)	25.1 ± 3.7
Diabetic Complications		
Eye Problem		
Yes	251 (31.8)	24.8 ± 3.5
No	539 (68.2)	24.9 ± 3.8
Kidney Problem		
Yes	86 (10.8)	24.3 ± 3.6
No	707 (89.2)	25.0 ± 3.8
Circulation Problem or Amputation		
Yes	292 (36.9)	24.5 ± 3.7
No	500 (63.1)	25.1 ± 3.8
Treatment Disease (Insulin Use)		
Yes	194 (24.2)	25.2 ± 3.7
No	609 (75.8)	24.8 ± 3.8
Disease Duration		
10 years	259 (33.6)	25.3 ± 3.6
≤10 years	511 (66.4)	24.7 ± 3.8

* p value <0.001; SD: standard deviation; MMSE: Mini Mental State Examination; CES-D: Center for Epidemiologic Studies Depression Scale; ADL: activities of daily living; BMI: body mass index

It is not clear why diabetes confers an increased risk of cognitive impairments, but several medical conditions that coexist with type-2 diabetes in older people have been implicated as risk factors for dementia. These include stroke, hypertension and depression.[11,12] For example, Wu and colleagues,[6] in a cohort of Latinos aged ≥60, found that greater cognitive decline is associated with presence of diabetic complications such as retinopathy, nephropathy, amputations and stroke. Boston and colleagues[13] found that significantly more subjects with vascular dementia had diabetes compared to subjects with Alzheimer's disease and nondemented subjects. MacKnight and colleagues[14] also found an association between diabetes and vascular cognitive impairment but not with Alzheimer's disease.

Few longitudinal studies, however, have examined risk factors for cognitive decline over time in patients with diabetes at the population level.[6,8-10,15] It is also not clear whether the risk of cognitive impairment is associated with type-2 diabetes or whether it is due to other conditions affecting cognitive function or treatment of diabetes. Possible reasons for inconsistent findings include tests that assess some but not all aspects of cognition, differences in the test sensitivity assessments of cognitive function, and differences in inclusion criteria and study design (time of observation, populations observed, statistical methods used). Very little is known about risk of cognitive decline in very old people, especially in the population with a very high prevalence of diabetes: the older Mexican Americans.

The purpose of this study is to examine predictors of cognitive decline over a seven-year period among older Mexican Americans with diabetes. This study is important in this population for several reasons. Mexican Americans with diabetes have greater fasting glycemia than non-Hispanic whites, higher prevalence of cogni-

Table 2. General linear mixed models estimates for cognitive decline among older Mexican Americans with diabetes (N=808)

Explanatory Variables	Model 1 Estimate (SE)	Model 2 Estimate (SE)
Intercept	24.63 (0.17)*	24.59 (0.17)*
Time (Years)	-0.38 (0.04)*	-0.32 (0.06)*
Age at Baseline (Years)	-0.09 (0.02)*	-0.09 (0.02)*
Gender (Male)	0.10 (0.25)	0.10 (0.27)
Education (Years)	0.36 (0.03)*	0.35 (0.03)*
Marital Status (Married)	0.63 (0.24)†	0.56 (0.26)‡
Hypertension	-0.80 (0.25)†	-0.72 (0.26)†
Stroke	-1.11 (0.36)†	-0.96 (0.42)†
Heart Attack	0.41 (0.31)	0.21 (0.35)
Depression (CES-D score)	-0.03 (0.01)‡	-0.01 (0.01)
Obesity (BMI ≥30 Kg/m^2)	0.11 (0.21)	0.03 (0.23)
ADL Limitations	-0.29 (0.07)*	-0.25 (0.10)*
Diabetic Complications		
Eye problem	-0.03 (0.23)	-0.26 (0.27)
Kidney problem	-0.60 (0.32)	-0.16 (0.38)
Circulation problem or amputation	-0.36 (0.23)	-0.11 (0.25)
Diabetic Treatment (Insulin Use)	-0.17 (0.25)	0.07 (0.28)
Disease Duration (≥10 Years)	1.04 (0.26)*	1.05 (0.27)*
Gender (Male) * Time		-0.15 (0.09)
Education (Years) * Time		0.003 (0.01)
Marital Status (Married) * Time		0.03 (0.09)
Hypertension * Time		-0.09 (0.11)
Stroke * Time		-0.06 (0.12)
Heart Attack * Time		0.15 (0.10)
Depression (CES-D score) * Time		-0.01 (0.004)‡
Obesity (BMI ≥30 Kg/m2) * Time		0.07 (0.08)
ADL Limitations * Time		-0.002 (0.03)
Diabetic Complications		
Eye problem * time		0.14 (0.08)
Kidney problem * time		-0.20 (0.10)‡
Circulation problem or amputation * time		-0.24 (0.09)†
Diabetic Treatment (Insulin Use) * Time		-0.15 (0.09)
Disease Duration (≥10 Years) * Time		-0.06 (0.08)

* p value <0.001; † p value <0.01; ‡ p value <0.05

tive impairment, severe peripheral macrovascular disease (such as limb amputations) and microvascular diseases (such as retinopathy and nephropathy) as well as higher rates of microalbuminuria and proteinuria.[16] Specifically, we examine whether the underlying pathogenesis of cognitive decline in subjects with diabetes should be attributed mostly to micro- and macrovascular diseases and whether the magnitude of difference in cognitive score between subjects with and without risk factors for dementia become clinically meaningful. Understanding factors associated with impaired cognition among older patients with diabetes is key toward the developing and testing of interventions to reduce or stop cognitive disability in this population.

METHODS

Sample and Procedures

Data used were from the Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE), a longitudinal study of Mexican Americans aged ≥65, residing in Texas, New Mexico, Colorado, Arizona and California. The sample and its characteristics have been described elsewhere.[17,18] The present study used baseline data (1993–1994) and data obtained from a two-year follow-up (1995–1996), a five-year follow-up (1998–1999) and a seven-year follow-up assessment (2000–2001). Of the 3,050 subjects interviewed at baseline, 879 subjects had a self-reported diagnosis of diabetes over the four waves. Excluding subjects with MMSE ≤17 at baseline yielded a final sample of 808 subjects: 600 subjects in the first wave, 100 subjects in the second wave, 65 subjects in the third wave and 43 subjects in the fourth wave. Subjects excluded (N=71) from the analysis were significantly more likely to be older; to have lower levels of education; to be unmarried; to have ever had a stroke, heart attack, high depressive symptoms, eye and kidney problems; or to be disabled. At the end of the follow-up (2000–2001), 462 (57.2%) subjects were reinterviewed, 29 (3.6%) subjects refused to be reinterviewed, 59 (7.3%) subjects were lost to follow-up, and 259 (31.9%) subjects were confirmed dead through the National Death Index (NDI) and reports from relatives.

MEASURES

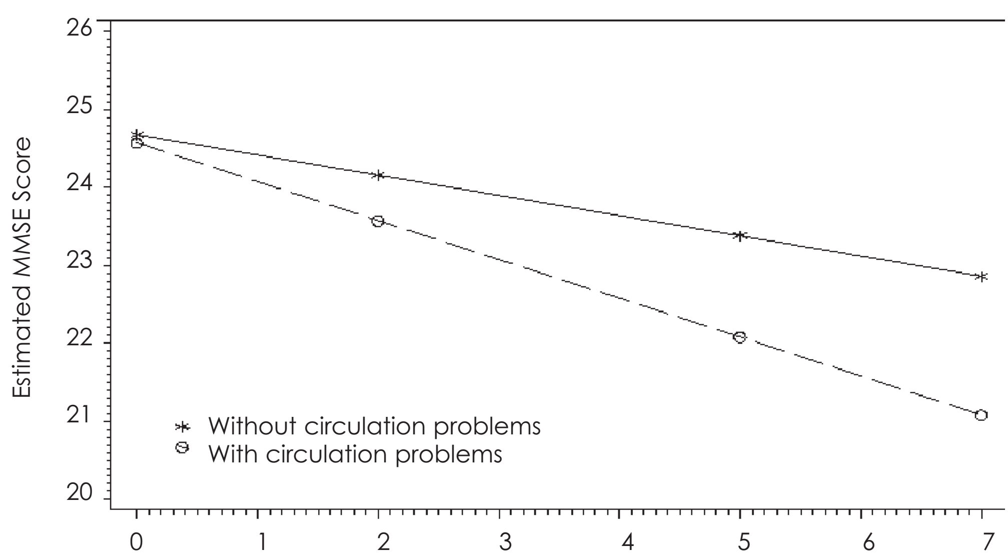
Diabetes Mellitus

We assessed diabetes by asking if subjects had ever been told by a doctor that they had diabetes. Respondents who reported a diabetes diagnosis were asked about disease duration (≤10 years vs. >10 years) and treatment received (categorized as: none, oral hypoglycemic, insulin or oral hypoglycemic/insulin combination). Respondents were asked if they had problems with their kidneys, eyes or circulation or if they have any amputations due to their diabetes.

Cognitive Function

Cognitive function was assessed with the Mini Mental State Examination (MMSE) instrument.[19-20] Interviewers were thoroughly trained in administration and scoring of the MMSE, both through workshops and videotaped instruction. The English and Spanish versions of the MMSE were adopted from the Diagnostic Interview Scale (DIS) used in prior community survey studies.[20] This Spanish version of the MMSE has met standard cri-

Figure 1. Predicted MMSE score over seven-year period for older Mexican Americans with diabetes with and without circulation problems (N=808)



teria for development of translated tests, including formal translation, back-translation and consensus by committee for final item content.[21] Additionally, the Spanish MMSE has been successfully used in community surveys of Mexican Americans.[22] Scores have a potential range of 0–30, with lower scores indicating poorer cognitive ability. Because of the low educational attainment and advanced age of our subjects (average education=4.9 years; average age=72.5), we identified individuals as having cognitive impairment if their MMSE score was <18 at baseline.[23] This study included only subjects with a MMSE cutoff score of ≥18, similar to past studies of populations with lower educational attainment and in certain ethnic minorities with low English literacy.[23]

Covariates

Baseline sociodemographic variables included age, gender, marital status and years of formal education. We assessed the presence of medical conditions by asking if respondents had ever been told by a doctor that they had hypertension, heart attack or stroke. Body mass index (BMI) was computed by dividing measured weight in kilograms by height in meters squared (Kg/m^2). Participants with BMIs of ≥30 were considered obese.[24]

Functional disability was assessed by seven items from a modified version of the Katz Activities of Daily Living (ADL) scale.[25] ADLs include walking across a small room, bathing, grooming, dressing, eating, transferring from a bed to a chair, and using the toilet. Any ADL limitation was dichotomized as: no help needed/needing help with or unable to perform ≥1 ADL activities. Depressive symptomatology was measured with the Center for Epidemiologic Studies Depression Scale (CES-D).[26] A score of ≥16 indicates high depressive symptomatology.[27]

Statistical Analysis

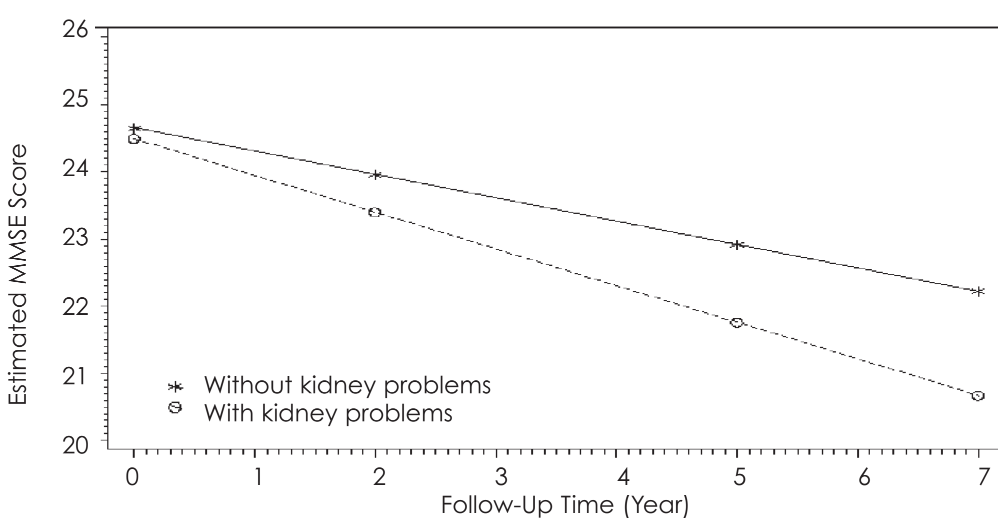
General linear mixed model using the MIXED procedure in SAS was used to examine the factors associated with decline in cognitive function over a seven-year period among older Mexican Americans with diabetes. All variables were analyzed as time-dependent covariates (potential to change as time progresses) except age, education and gender. The mixed model was chosen for analysis because it best handles unbalanced data, allowing for modeling of time-dependent change in variables as well as time-dependent change in magnitude of association between variables. Also, because H-EPESE data comprised repeated measures over seven years, mixed models allow for more flexibility in modeling the effects of time on outcome.[28-29]

Two mixed models were constructed to test the relationship between the predictor variables and cognitive decline over the seven-year period. Model 1 included age, gender, marital status, years of formal education and time. Model 2 included interaction terms (each predictor variable x time), medical conditions, ADL limitations, high depressive symptoms, BMI, diabetic complications and disease duration along with the variables in Model 1. Interaction terms assess the association between each predictor variable and slope of cognitive function over time. The time interactions represent the estimated effect of each predictor variable on rate of change in cognitive function. All analyses were performed using the SAS System for Windows®, Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows baseline characteristics and mean ± standard deviation (SD) of MMSE score for older Mexican Americans with diabetes. The average MMSE score

Figure 2. Predicted MMSE score over seven-year period for subjects with and without kidney problems (N=808)



for subjects in the study was 24.9 with SD of 3.8 point. The mean age of the sample was 72.6 years, 485 (60%) of the respondents were women and 472 (58.4 %) were married. Mean level of education was 4.9 years. The most common medical conditions were hypertension (71.8%) and stroke (8.0%), 24.4% had high depressive symptoms (CES-D ≥16), 14.5% reported any ADL limitations and 39.2% had a BMI ≥30 Kg/m^2. Circulation problems or amputations were reported in 36.9% subjects, eye problems in 31.8% subjects and kidney problems in 10.8% subjects. Insulin alone or in combination with hypoglycemic agents was used by 24.2% of subjects, 565 (70.4%) used oral hypoglycemics only and 44 (5.9%) were diet controlled only. Diabetes duration >10 years was reported in 33.6% of the subjects. There were no statistical differences in MMSE score at baseline for each predictor variable except for years of education (<8 years = 24.2 ± 3.7 vs ≥8 years = 27.1 ± 3.2; p value <0.001).

Table 2 presents the general linear model estimates for change in MMSE score as a function of covariates (sociodemographic factors, medical conditions, diabetic complications, disease duration and treatment received). In Model 1, the rate of decline in cognitive function was 0.38 per year. Subjects with high level of education [estimate = 0.36, standard error (SE) = 0.03], married (estimate = 0.63, SE = 0.24), and those with a disease duration ≥10 years (estimate = 1.04, SE = 0.26) were significantly associated with higher MMSE score at each point time of follow-up (intercept of MMSE score). Older age (estimate = -0.09, SE = 0.02), hypertension (estimate = -0.80, SE = 0.25), stroke (estimate = -1.11, SE = 0.36), high depressive symptoms (estimate = -0.03, SE = 0.01) and increasing ADL limitations (estimate= -0.29, SE = 0.07) were significantly associated with lower MMSE score at each follow-up (intercept of MMSE score).

In Model 2, interaction terms were added. There was a significant interaction term between covariates and time (slope of MMSE score over time) in subjects with high depressive symptoms (estimate = -0.01, SE = 0.004), kidney problem (estimate = -0.20, SE = 0.10), and circulation problem (estimate = -0.24, SE = 0.06), indicating that subjects with depression and diabetic complications (kidney and circulation problems) had greater decline in MMSE score over time when compared with those without these complications.

To better illustrate and understand the decline in MMSE scores associated with diabetic complications, slopes of change in MMSE scores were created for every evaluated factor significantly associated with change in cognition over time in comparison to the reference slope. Figures 1 and 2 show the estimated MMSE score over a seven-year period for subjects with circulation problems or amputation and kidney problems for those subjects with diabetes over the four waves. Steepness of slope indicates the rate of cognitive decline. No significant differences in baseline MMSE scores are observed.

DISCUSSION

This study examined social, demographic and health factors associated with cognitive decline over seven years among older Mexican Americans with diabetes. Over the seven-year period of observation, having diabetic complications (circulation and kidney problems) and depression were the major factors associated with cognitive decline in older Mexican Americans with diabetes. Despite adjustment for prevalent comorbidities, these associations remained statistically significant.

Our study is comparable with previous studies conducted using the MMSE among older subjects with diabetes, but it also extends the results of previous longitudinal studies. Past research suggests that diabetes coexisting with hypertension or stroke accelerates cognitive decline. Haan and colleagues,[11] in a cross-sectional study of community-dwelling elderly people ≥60 years, found that Hispanic and non-Hispanic whites alike have poorer cognitive performance in MMSE score when diabetes coexists with a history of stroke. Using data from the Framingham Heart Study, Elias and colleagues[10] found that those with both diabetes and hypertension had poorer performance on tests of visual organization and memory, while normotensives with diabetes did not. They also found that patients on insulin performed worse in some neuropsychological tests involving verbal and visual memory.

No previous longitudinal studies, to our knowledge, have looked specifically at the relationship between peripheral vascular disease or kidney impairment and cognitive function in subjects with diabetes. Indeed, few studies in the general population have explored the association of peripheral vascular disease with cognitive impairment.[30] Little is known about kidney impairment and cognitive performance,[31] and no study to our knowledge has examined the latter in older diabetics with nephropathy. Our research shines a new light on the impact of diabetic complications (peripheral vascular disease and nephropathy, but not retinopathy) on the decline in cognitive function.

It is well known that peripheral vascular disease is a risk factor for minor ischemic stokes and transit ischemic attacks (TIA). Peripheral vascular disease also adversely affects stroke outcomes. Peripheral vascular disease is a marker of generalized atherosclerosis. Moreover, this disease is often asymptomatic and underdiagnosed, as is kidney dysfunction. As our study indicates, by the time diagnosis is made, patients may already have significant loss of cognitive function. Therefore, effort should be concentrated on early detection of peripheral vascular disease and nephropathy by screening patients with diabetes with ankle-brachial index (for signs of peripheral vascular disease) and on urine analysis for microproteinuria; both tests are relatively inexpensive. Next, aggressive management with antiplatelet medication (aspirin, clopidogrel), statins, and optimal control of blood pressure and proteinuria by use of ACE inhibitors may slow progression of cognitive decline in older subjects with diabetes.

This study has some limitations. First, the assessment of diabetes mellitus and its complications was by self-report. Clinical observation may provide a different and more precise diagnosis. However, the self-report approach has been documented to provide reliable information and a good agreement between self-reported diabetes and diabetes diagnosed by blood tests.[32] Second, by including in the sample subjects who were reinterviewed, we are examining the cohort of survivors over a seven-year period. Subjects who were not interviewed at the last follow-up were significantly more likely to be male; to report high depressive symptoms, ADL disability, longer diabetes duration; to be in treatment with insulin; to have a BMI <30 Kg/m^2; and to have more eye, kidney and circulation problems when compared with those who were reinterviewed at the seven-year follow up. Third, cognitive function is established by MMSE scores, which may not reflect all cognitive functions, especially executive function. However, using conventional cut-off scores with adjustment for confounders, the MMSE has consistently yielded correct classification rates of 80–90% when compared with physician assessment of cognitive impairment and dementia.[22] Our study has several strengths, including its large community-based sample, its prospective design and its exploration of potential factors affecting cognitive function in older Mexican Americans—a rapidly growing segment of the older population. Another important strength is the use of mixed models, an analytic approach that allows use of all available data and evaluation of time-dependent effects. By excluding severely impaired individuals, we were able to see a less rapid decline in MMSE for the group and to better estimate risk factors for decreased cognitive function.

This is the first study to demonstrate that in older Mexican Americans living with diabetes, circulation and kidney problems are major risk factors for cognitive decline over time. Our study also underscores the difference between factors influencing baseline cognition versus those factors influencing rate of cognitive decline, a difference that future intervention studies should consider. In conclusion, increasing awareness of the associations among diabetes-related complications of circulation problems, kidney problems, and depression and cognitive decline can help clinicians screen for and manage these complications with the goal of preserving cognitive function and independent living in elderly patients with diabetes.

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