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Does type 2 diabetes increase rate of cognitive decline in older Mexican Americans?

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Abstract

Estimating effects of diabetes on cognitive change among older Mexican Americans is important, yet challenging because diabetes and cognitive decline both predict mortality, which can induce survival bias. Older Mexican Americans in the Sacramento Area Latino Study on Aging (n=1,634) completed Modified Mini-Mental State Exams (3MSE) and diabetes assessments up to seven times (1998-2007). We examined baseline and new onset diabetes and cognitive decline with joint longitudinal-survival models to account for death. At baseline, 32.4% of participants had diabetes and 15.8% developed diabetes during the study. Over the study, 22.8% of participants died. In joint longitudinal-survival models, those with baseline diabetes experienced faster cognitive decline (p=0.003) and higher mortality (HR=1.88, 95% CI 1.48-2.38) than those without diabetes. Cognitive decline and mortality were similar for those with new onset diabetes and those without diabetes. For a typical person, 3MSE scores declined by 2.3 points among those without diabetes and 4.3 points among those with baseline diabetes during the last 6 years of study. Ignoring the impact of death yielded a 17.0% smaller estimate of the effect of baseline diabetes on cognitive decline. Analyses that overlook the association between cognitive decline and mortality may underestimate the effect of diabetes on cognitive aging.

Introduction

Cognitive decline and dementia are major causes of disability and death for older adults[1], and strategies to prevent or treat dementia remain elusive. A growing body of evidence suggests that older adults with type 2 diabetes are 50-100% more likely to develop dementia than those without diabetes[2,3]. Type 2 diabetes is a growing epidemic in the United States and globally[4] Certain racial and ethnic groups, including Mexican Americans, experience a disproportionate burden of diabetes. However, there is very limited research on dementia and related outcomes among this potentially vulnerable minority population.

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To understand whether diabetes contributes to dementia pathogenesis, it is important to examine the association between diabetes and rate of cognitive decline. Dementia onset is influenced by both level of cognitive function prior to onset of decline and rate of cognitive decline. Thus, the association between diabetes and dementia could be confounded by shared determinants of diabetes and level of cognitive function prior to onset of decline, such as early life social factors. Findings on diabetes and rate of cognitive decline have been inconsistent: many studies report an association between diabetes and decline in one or more domains, but across studies, there is not a consistent association between diabetes and cognitive decline[5-8]. A recognized methodological limitation that could contribute to inconsistent results of prior work is selective survival. Since both diabetes[9] and accelerated cognitive decline[10,11] are associated with higher mortality, ignoring attrition due to death may lead to underestimation of the effect of diabetes on cognitive decline. Although the potential bias from selective survival is well understood, few prior studies of diabetes and cognitive change have implemented statistical tools to account for this bias. To address gaps in the existing literature on the effects of diabetes on cognitive aging, this study will examine the effect of type 2 diabetes on rate of cognitive change while accounting for mortality over up to ten years among older Mexican Americans.

Methods

Study population

The Sacramento Area Latino Study on Aging (SALSA) is a population-based longitudinal study of older Mexican Americans living in the Sacramento Valley area of California who were 60-101 years old at baseline in 1998-1999. SALSA was designed to examine the effects of metabolic and cardiovascular risk factors on dementia and cognitive decline in this understudied ethnic group. A total of 1,789 participants were interviewed and underwent clinical examinations, including a cognitive assessment, in their homes every 12-15 months through 2007 for up to seven examinations. Participants were also contacted every six months by telephone to update contact information and health status. Study questionnaires were validated in Spanish and English, and interviews were conducted in the language that participants preferred. A detailed description of study procedures has been published previously[12]. SALSA was approved by the Institutional Review Boards of the University California San Francisco and Davis and the University of Michigan.

Measures

Type 2 diabetes—At every study visit, diabetes classification was based on fasting glucose level ≥126 mg/dL, anti-diabetic medication use, or self-report of a physician diagnosis of diabetes at the baseline examination. Fasting glucose was measured with the Cobas Mira Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN) and medication use was ascertained by inspection of medications. The majority (75.5%) of participants with diabetes at baseline met at least two criteria and 24.5% met one (10.8% fasting glucose level, 2.1% medication use, and 11.7% self-report). Due to the advanced age of the cohort, most diabetes cases are likely to be type 2 diabetes. At each wave, individuals were designated as having one of the following: baseline diabetes, diabetes at the current wave that was diagnosed since baseline (diabetes diagnosed during study), or no diabetes.

Cognitive function—Cognitive function was assessed every 12-15 months with the Modified Mini Mental State Exam (3MSE). The 3MSE is a test of global cognitive function that was designed to have fewer ceiling effects and better reliability and validity than the Mini-Mental State Examination[13]. Scores on the 3MSE range from 0-100, where higher test scores indicate better cognitive function. The distribution of 3MSE scores was left-skewered. As such, we examined the log-transformation of the errors on the 3MSE (log(101 –3MSE score)) to correspond more closely to a normal distribution. More errors indicate poorer cognitive function, and an increase in log(3MSE errors) over time indicates cognitive decline.

Death—Ascertaining mortality involved the following methods: online surveillance of death notices, review of the Social Security Death Index, the National Death Index, vital statistics data files from the state of California, and interviews with family members when participants could not be reached for annual study visits or interim six month phone calls. This analysis is restricted to deaths during active follow-up for the study (1998-2007).

Other variables—At baseline, age, sex, years of education, country of birth, and history of stroke, myocardial infarction, congestive heart failure, angina pectoris, atrial fibrillation, intermittent claudication, and deep vein thrombosis were collected from a structured baseline interview. Waist circumference, height, weight, blood pressure, and depressive symptoms were measured. Waist circumference was measured around the point of greatest indentation on the abdomen when the participant bent to one side, and categorized according to American Heart Association sex-specific cut-points for abdominal obesity (>40 inches for males, >35 inches for females)[14]. BMI (kg/m^2) was calculated from direct measurements of height and weight. Hypertension was defined based on measured systolic blood pressure >140 mmHG or diastolic blood pressure >90 mmHG, self-report of a physician diagnosis, or anti-hypertensive medication use. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression (CESD) Scale, a widely used scale (range 0–60), and elevated depressive symptoms was defined as CESD≥16[15]. Cardiovascular disease was defined as history of one or more of the following conditions: myocardial infarction, congestive heart failure, angina pectoris, atrial fibrillation, intermittent claudication, and deep vein thrombosis.

Statistical analysis

To examine the association between diabetes status and rate of change in cognitive function while accounting for the dependence between cognitive decline and death, we used a joint longitudinal-survival model[16] to simultaneously model cognitive decline and risk of death. This modeling approach corrects for selective survival to the extent that the model recovers the association between diabetes and cognitive function that would have been obtained using a separate linear mixed effects model if mortality were independent of rate of cognitive change. The joint model was comprised of two sub-models that use a shared parameter for rate of cognitive change (random effect for slope): a sub-model for repeated measures of cognitive function (linear mixed effects model with random effects for intercept and slope[17].) and a sub-model for time to death (piecewise exponential model[18]). We ran the joint models using PROC NLMIXED following the approach described by Guo and

Carlin[19]. In both sub-models, diabetes was modeled as a time-dependent variable: at each wave, individuals were designated as having baseline diabetes, diabetes at the current wave that was diagnosed since baseline diabetes, or no diabetes. Both sub-models used time (in years) from enrollment as the time scale. For the piecewise exponential sub-model, we divided the time scale into five two-year intervals because this division corresponded reasonably well with the spacing of the cognitive assessments and the hazard function appeared relatively constant within each two-year interval.

In the linear mixed effects sub-model, we included indicators for the first and second testing occasions to account for practice effects, which were evident when we examined average 3MSE scores at each visit among participants who remained under study through the final assessment. Practice effects (also called retest or learning effects) refer to improvements in cognitive test performance attributable to increased familiarity with the cognitive testing procedures, and have been demonstrated in other studies of older adults with cognitive assessments administered a year or more apart[20,21]. Accounting for the practice effect improved the model fit over a simple linear or linear quadratic model form. We estimated the difference in average annual rate of change in cognitive function associated with diabetes with a multiplicative interaction term between diabetes status and time in years (baseline diabetes*time and diabetes diagnosed during study*time).

We fit a series of models to assess the joint effects of diabetes on cognitive decline and mortality. First, we fit a model with diabetes as the only predictor (Model 1). Next, we included age, sex, and years of education (Model 2). Finally, we additionally adjusted for baseline abdominal obesity, history of stroke, hypertension, history of cardiovascular disease, and elevated depressive symptoms (Model 3). For ease of interpretation, all continuous variables were centered at the mean baseline value for the study sample.

To handle missing data, we used imputed data for variables missing for individuals prior to exit from the study (either due to death or censoring). A multiple-imputation approach was performed using the entire SALSA dataset to develop predictive models for missing data[22]. Five imputed datasets were created using Imputation and Variance Estimation Software[23]. The results from regression analyses from the five imputed datasets were summarized using the MI ANALYZE procedure.

All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Participants were followed from enrollment in 1998-1999 through 2007. A total of 1,789 participants enrolled in SALSA. Participants with dementia at baseline (n=87) and those lost to follow-up after only the baseline visit (n=68) were eliminated from analysis. The resulting sample size was 1,634 individuals.

The median follow-up time was 7.6 years (interquartile range: 4.8-8.2). A total of 530 (32.4%) had diabetes at baseline and an additional 258 (15.8%) developed diabetes during the study. Throughout the study, 372 (22.8%) participants died and 335 (20.5%) participants were lost to follow-up.

At baseline, participants with diabetes were more likely to have been born in the U.S., have higher BMIs, and have a higher prevalence of abdominal obesity, hypertension, history of stroke, and history of cardiovascular disease (Table 1). At baseline, 64.2% of participants with baseline diabetes were using an anti-diabetic medication. Among participants who developed diabetes during the study, the majority (75.7%) were not using an anti-diabetic medication at the visit of diagnosis.

Individuals with baseline diabetes experienced substantially faster cognitive decline compared to those without diabetes, and baseline diabetes and rate of cognitive change were both associated with an increased risk of death (Table 2). New onset diabetes was not associated with rate of cognitive change or death. Adjustment for potential confounders had little impact on estimates of cognitive change. For example, for a typical person, 3MSE scores declined by 2.3 points among those without diabetes and 4.3 points among those with baseline diabetes during the last 6 years of follow up, and a standard deviation increase in rate of cognitive change was associated with 73% higher rate of death. Figure 1a illustrates predicted 3MSE score trajectories from Model 3 estimates for an individual with baseline diabetes, an individual who developed diabetes at year 4.5 in the study, and an individual who remained free of diabetes throughout the study period. An individual identified as having diabetes at the year 4.5 of the study remains in the no diabetes group until the cognitive assessment at year 3 and is part of the new onset diabetes group from year 4.5 forward. Overall, 3MSE scores increased through the third assessment, which we attribute to practice effects, and declined thereafter. Results from a separate linear mixed effects model for cognitive decline estimated a 17.0% smaller effect of baseline diabetes on rate of cognitive change (coefficient for baseline diabetes*time (in years): b=0.018, 95% CI 0.004-0.032) compared to the joint model for cognitive decline and death (Supplementary Table).

We further examined 3MSE score trajectories among participants who died during the study and those who survived with mixed linear effects models adding two-way interactions between death and time and death and diabetes status and three-way interactions among death, time, and diabetes status. Figure 1b illustrates the trajectories of change in 3MSE scores by diabetes status among participants who survived and those who died during the study period. Although the interaction terms with death were non-significant (death*time p=0.020, death*time*baseline diabetes p=0.11, death*time*new onset diabetes p=0.90), the observed trend was that rate of cognitive decline was faster among participants who died compared to those who survived, particularly for those with baseline diabetes.

Discussion

In this cohort of older Mexican Americans, those with prevalent diabetes at baseline experienced faster rates of cognitive decline than those without diabetes, but new onset diabetes was not associated with rate of cognitive decline. Baseline diabetes and faster rate of cognitive decline were both associated with an increased risk of death. Conventional models yielded smaller estimates of the effect of baseline diabetes on rate of cognitive decline compared to joint longitudinal-survival models, which account for the dependence between cognitive decline and mortality.

Our finding that separate longitudinal models estimated smaller effects of baseline diabetes on rate of cognitive decline compared to joint longitudinal-survival models suggests that conventional estimation techniques underestimate the effect of diabetes on rate of cognitive decline because diabetes and cognitive decline both predict mortality. This suggests that the effect of diabetes on rate of cognitive decline may have been underestimated in prior studies. Jointly modeling rate of cognitive decline and mortality in observational studies may be useful for planning future intervention studies for prevention of dementia. While the potential bias from selective survival has been widely recognized by researchers studying cognitive decline, few studies have attempted to address this issue. Future studies are needed to further quantify the potential degree of bias from selective survival in research on the effects of diabetes, as well as other exposures, on cognitive decline.

We previously found that diabetes is associated with a two-fold increased incidence of cognitive impairment and dementia in this same cohort[24]. Several previous studies examining the association between baseline diabetes and cognitive decline in non-Hispanic white and African American populations have found that diabetes is associated with greater cognitive decline in one or more cognitive domains among older adults[5,8,25-28], although a few studies have reported no association[7,29]. Our finding that new onset diabetes was not associated with rate of cognitive decline is consistent with other recent studies showing that longer diabetes duration is associated with cognitive decline[5,6,8,28,30]. However, several of these studies found that the rate of cognitive decline among individuals who developed diabetes throughout the study fell between that of individuals who remained free of diabetes and those with baseline diabetes in one or more cognitive domain[5,8,30]. It is possible that certain cognitive domains are more sensitive to the effects of the early stages of diabetes, but the present study only measured global cognitive function. Characteristics of the study populations, length of study, and specific neuropsychological tests used may also contribute to differences in results across studies. The association between diabetes and cognitive decline over two years has previously been examined in SALSA[31]; no differences in change in cognitive function by diabetes status were observed over this short follow-up. To our knowledge, the Hispanic Established Populations for the Epidemiological Study of the Elderly is the only other study that has examined diabetes and change in cognitive function among older Mexican Americans[32]. The authors found that self-reported diabetes was associated with a higher risk of severe cognitive impairment but not moderate impairment over five years.

While our study addresses some of the biases of prior studies, it also has several limitations. Although mortality was the primary source of attrition in this cohort, some non-mortality attrition was present, and participants with diabetes and those beginning to experience cognitive decline may have been more likely to withdraw from the study, which could lead to underestimation of the effect of diabetes on cognitive decline. The 3MSE is a test of global cognitive function, so inferences about the effects of diabetes on specific cognitive domains cannot be drawn from this study.

The results of this study are nonetheless generalizable to community-dwelling older Mexican Americans, as well as other populations with similar risk factor profiles and mortality rates. SALSA is a longitudinal population-based study, and participants were

representative of community-dwelling older Mexican Americans living in the Sacramento Area in 1998-1999[12]. Study interviews and the 3MSE were validated in both English and Spanish.

In this population-based study of older Mexican Americans, we found that individuals with baseline diabetes experienced faster rates of cognitive decline than those without diabetes, but diabetes diagnosed after baseline was not associated with rate of cognitive decline during the study. Furthermore, our results suggest that conventional analysis approaches, which do not account for the dependence between cognitive decline and mortality, may underestimate the effect of diabetes on rate of cognitive decline. Our results are germane to potential public health interventions, as they suggest that prevention and management of diabetes could be successful strategies to preserve cognitive function and prevent dementia in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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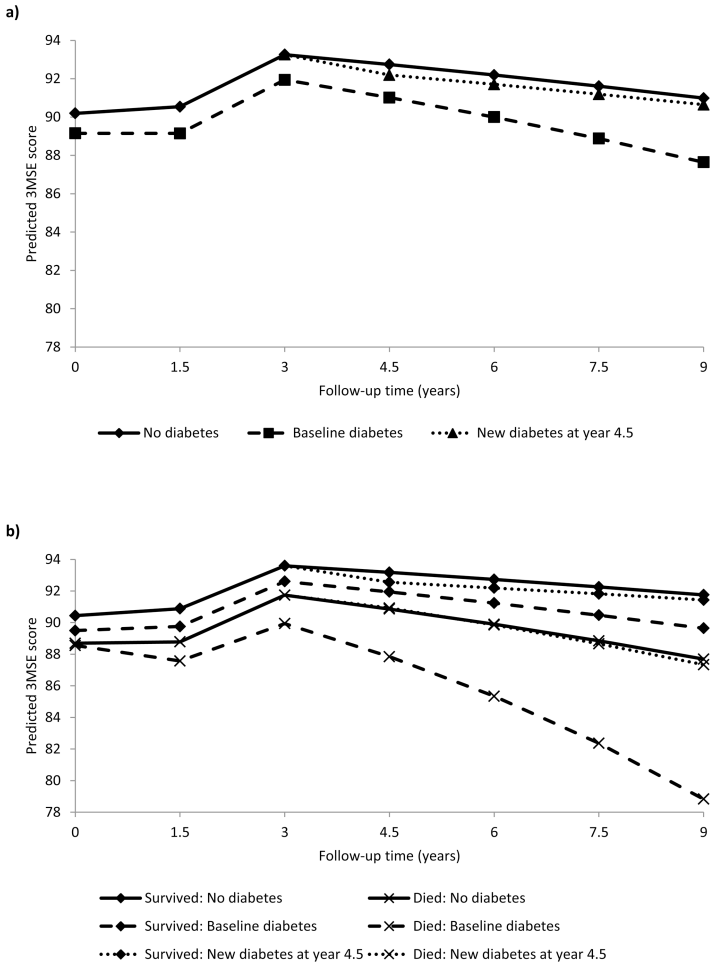

Figure 1.

Predicted 3MSE scores from a) the joint longitudinal-survival model to describe the association between diabetes and rate of change in cognitive function and b) from the mixed linear effects model to describe the association between diabetes and rate of change in cognitive function by survival status. Predictions are for an individual who remains free of diabetes throughout the study (solid line), an individual with baseline diabetes (dashed line), and an individual with new diabetes at year 4.5 of the study (dotted line). All predictions are for a male individual 70 years of age with 7 years of education, waist circumference <40 inches, no history of stroke or cardiovascular disease, without hypertension or elevated depressive symptoms.

Table 1

Baseline characteristics of the sample by baseline diabetes status (n=1,634).

Variable	No diabetes (n=846)	Baseline diabetes (n=530)	Diabetes diagnosed after baseline (n=258)	p-value
	mean (SD) or %	mean (SD) or %	mean (SD) or %	
Age (years)	71.0 (7.1)	69.9 (6.5)	68.9 (6.0)	<0.001
Education (years)	7.6 (5.3)	7.3 (5.4)	7.3(5.3)	0.525
Female sex	59.7	55.5	56.6	0.276
Born in U.S.	47.6	56.4	45.0	0.001
Body mass index (kg/m2)				<0.001
<25	25.1	12.3	14.7	
25-30	37.6	37.9	37.6	
≥30	37.4	49.8	47.7	
Abdominal obesity	43.6	61.7	57.8	<0.001
Hypertension	61.9	81.7	70.9	<0.001
Stroke	6.4	13.0	5.4	<0.001
Cardiovascular disease	22.7	40.8	29.1	<0.001
Elevated depressive symptoms	23.3	27.4	23.6	0.214

Abdominal obesity defined as waist circumference >40 inches for males, >35 inches for females. Hypertension defined as systolic blood pressure >140 mm HG or diastolic blood pressure >90 mmHG, self-report of a physician diagnosis, or anti-hypertensive medication use. Cardiovascular disease includes self-report of myocardial infarction, congestive heart failure, angina pectoris, atrial fibrillation, intermittent claudication, or deep vein thrombosis. Elevated depressive symptoms defined as Center for Epidemiological Studies-Depression Scalescore ≥16. ANOVA was used for continuous variables, chi-square tests were used for categorical variables; p-values are two-sided.

Table 2

Regression coefficients (b) to describe the association between diabetes and rate of change in cognitive function (log(errors on Modified Mini Mental State Exam)) and hazard ratios (HR) to describe the associations of diabetes and rate of cognitive change with risk of death from joint longitudinal-survival models.

	Model 1			**Model 2**			**Model 3**		
Longitudinal sub-model									
Parameter	b	95% CI	p-value	b	95% CI	p-value	b	95% CI	p-value
Intercept	1.919	(1.857, 1.982)	<0.001	1.939	(1.874, 2.003)	<0.001	1.918	(1.836, 2.000)	<0.001
Wave 1 indicator	0.471	(0.412, 0.53)	<0.001	0.463	(0.404, 0.522)	<0.001	0.462	(0.403, 0.521)	<0.001
Wave 2 indicator	0.369	(0.312, 0.426)	<0.001	0.366	(0.309, 0.423)	<0.001	0.365	(0.309, 0.422)	<0.001
Baseline diabetes	0.112	(0.036, 0.188)	0.004	0.103	(0.042, 0.164)	<0.001	0.092	(0.030, 0.154)	0.003
Diabetes diagnosed during study	0.087	(-0.083, 0.257)	0.317	0.098	(-0.070, 0.266)	0.253	0.096	(-0.074, 0.265)	0.269
Time (years)	**0.058**	**(0.044, 0.072)**	**<0.001**	**0.045**	**(0.030, 0.060)**	**<0.001**	**0.043**	**(0.024, 0.062)**	**<0.001**
Baseline diabetes*Time	**0.024**	**(0.009, 0.038)**	**0.001**	**0.024**	**(0.010, 0.038)**	**<0.001**	**0.022**	**(0.007, 0.036)**	**0.003**
Diabetes diagnosed during study* Time	**-0.010**	**(-0.038, 0.017)**	**0.463**	**-0.008**	**(-0.036, 0.020)**	**0.584**	**-0.007**	**(-0.035, 0.021)**	**0.629**
Survival sub-model									
Parameter	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Baseline diabetes	2.19	(1.69, 2.84)	<0.001	2.19	(1.72, 2.79)	<0.001	1.88	(1.48, 2.38)	<0.001
Diabetes diagnosed during study	0.64	(0.33, 1.26)	0.193	0.71	(0.38, 1.32)	0.277	0.70	(0.36, 1.35)	0.278
log(3MSE errors) slope (1 SD* unit)	**2.79**	**(2.12, 3.68)**	**<0.001**	**1.80**	**(1.45, 2.24)**	**<0.001**	**1.73**	**(1.39, 2.16)**	**<0.001**

*SD=standard deviation. Model 1: unadjusted; Model 2: adjusted for age, sex, and years of education; Model 3: Model 2 + abdominal obesity, stroke, hypertension, cardiovascular disease, and elevated depressive symptoms.