Title

Type 2 Diabetes, Risk of Dementia and Cognitive Decline, and the Competing Risk of Mortality Among Middle-Aged and Older Adults

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Type 2 Diabetes, Risk of Dementia and Cognitive Decline, and the Competing Risk of Mortality Among Middle-Aged and Older Adults

by

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DISSERTATION

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Dedication and Acknowledgements

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A version of Chapter 1 of this dissertation has been published in *Diabetes Care*[1]. The Dissertation Committee members supervised the research that forms the basis of this dissertation chapter and are listed as coauthors in this publication. The published material is substantially the product of Elizabeth Rose Mayeda's period of study at UCSF and was primarily conducted and written by her. The work she completed for this published manuscript is comparable to a standard dissertation chapter.

Approved: Mary N Haan Mary N. Haan, DrPH, MPH, Dissertation Chair

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Type 2 Diabetes, Risk of Dementia and Cognitive Decline, and the Competing Risk of Mortality Among Middle-Aged and Older Adults

Elizabeth Rose Mayeda

Abstract

Type 2 diabetes is highly prevalent and has been linked with an increased risk of dementia and premature mortality. Earlier death among people with diabetes may impact the association between diabetes and dementia. This is particularly important for populations with a high burden of diabetes, including Mexican Americans and African Americans. The objective of this dissertation was to evaluate the association of diabetes with incidence of dementia and cognitive impairment without dementia (CIND) and cognitive decline in late-life among Mexican Americans and in mid-life among African Americans and whites while accounting for the competing risk of mortality. The study populations included: 1) a cohort of dementia-free older Mexican Americans (n=1617) aged 60-98 from the Sacramento Area Latino Study on Aging (SALSA) followed for 10 years beginning in 1998 and 2) a cohort of middle-aged African Americans and whites (n=1886) aged 48-70 from the Atherosclerosis Risk in Communities (ARIC) Study followed for 14 years beginning in 1990. The association between diabetes and incidence of dementia/CIND was examined with competing risk regression models in the SALSA cohort and the association between diabetes and cognitive decline was examined with joint longitudinal-survival models in the SALSA and ARIC cohorts. In the SALSA cohort, Mexican Americans with treated and untreated diabetes had an increased risk of dementia/CIND compared to those without diabetes (HR=2.05, 95% CI: 1.41-2.97 and HR=1.55, 95% CI: 0.93-2.58) after accounting for the competing risk of death. Additionally, Mexican Americans with diabetes experienced modestly accelerated cognitive decline compared to those without diabetes. In the ARIC cohort, earlier onset of diabetes was associated with greater cognitive decline in mid-life among African Americans. No

association between diabetes and cognitive decline was observed among whites. These findings provide evidence that the association between diabetes and dementia/CIND among Mexican Americans remains strong after accounting for the competing risk of mortality. The association between diabetes and cognitive decline is less evident. Future research is needed to identify how diabetes treatments influence cognitive decline among people with diabetes.

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Chapter 1: Type 2 diabetes and 10 year risk of dementia and cognitive impairment among older Mexican Americans

Introduction

Type 2 diabetes is a common and established risk factor for vascular disease and mortality [1]. Prevalence of type 2 diabetes is higher among older adults, and several minority racial/ethnic groups in the U.S. are disproportionally affected. Several prospective epidemiologic studies have found that older adults with type 2 diabetes have approximately a two-fold increased risk of dementia [2-9], but others have not [10-13], and the mechanism is controversial [14, 15]. Possible mechanisms linking type 2 diabetes to dementia and cognitive impairment include chronic hyperglycemia or hypoglycemia, hyperinsulinemia or insulin resistance, effects of inflammatory cytokines and oxidative stress, and beta-amyloid deposition in the brain [14, 15]. The type 2 diabetes-dementia association has not been evaluated among Mexican Americans, a population with a high prevalence of type 2 diabetes [16], poor glycemic control among those with diabetes [17], and higher rates of complications compared to non-Hispanic whites [18].

Mortality occurs at younger ages among people with type 2 diabetes [19]. Mortality rates are nearly twice as high among people with type 2 diabetes compared to people without diabetes [19-21]. Cognitive decline is also associated with higher mortality rates [22, 23]. Premature death in those with diabetes may influence the risk of dementia or cognitive impairment associated with type 2 diabetes. Previous studies of the association between type 2 diabetes and dementia have not accounted for competing risk of death. In this paper, we evaluate the association between type 2 diabetes and incidence of dementia and cognitive impairment without dementia (CIND) in a cohort of older Mexican Americans followed for ten years, accounting for the competing risk of death.

Methods

Study population

Participants included in this analysis were from the Sacramento Area Latino Study on Aging (SALSA), a cohort study of community-dwelling older Mexican Americans in the Sacramento Area of California designed to evaluate the effects of metabolic and cardiovascular risk factors on dementia in this understudied ethnic group. Recruits were eligible to participate in this study if they were aged 60 years or older at enrollment in 1998-99, resided in a six county area in the Sacramento Valley (Sacramento, Yolo, Sutter, Solano, San Joaquin, and Placer counties), and self-identified as Latino. A detailed description of study sampling and procedures has been published elsewhere [24]. A total of 1,789 participants enrolled between 1998 and 1999 were interviewed in their homes every 12-15 months for up to seven study visits ending in 2007. Every six months between home visits, a ten minute phone call was made to update contact information, health status, and medication changes. All participants provided written informed consent. SALSA has been approved annually by the Institutional Review Boards of the University of California at San Francisco and Davis and the University of Michigan.

Diabetes

At each study visit, diabetes classification was based on fasting glucose level ≥126 mg/dL, anti-diabetic medication use, or self-reports of a physician diagnosis at any study visit prior to dementia/CIND, death, or last study visit. Diabetic medications were recorded at every study visit by direct visual inspection of medications and classified using the Centers for Disease Control Ambulatory Care Drug Database (http://www2.cdc.gov/drugs/). Given the advanced age of the cohort, most, if not all, cases were probably type 2 diabetes [16]. Hereafter, we will use the term "diabetes" to refer to "type 2 diabetes."

Dementia and Cognitive Impairment without Dementia (CIND)

The classifications of dementia and CIND were determined at all home visits by a multistage assessment protocol, which has been described extensively elsewhere [24]. Briefly, at each visit, two cognitive screening tests were used to determine the need for further neuropsychological evaluation: the Modified Mini-Mental State Exam (3MSE) [25], a global cognitive function test, and a delayed word recall trial (DelRec) from the Spanish English Verbal Learning Test (SEVLT) [26], a word-list learning and memory test. At baseline, a participant was referred for further evaluation if his or her score on either test fell <20th percentile. At follow-up, a participant was referred for a neuropsychological test battery and a standard neuropsychological examination by a geriatrician if his or her follow-up score declined from the baseline score by >8 points on 3MSE or >3 points on SEVLT and the score fell below the 20th percentile. A team of neurologists and a neuropsychologist reviewed all potential dementia and CIND cases and classified participants as demented, CIND, or cognitively normal. Standard diagnostic criteria were applied for dementia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) [27], Alzheimer's disease (National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association) [28], and vascular dementia (California Alzheimer's Disease Diagnostic and Treatment Centers) [29]. Dementia and CIND cases were referred for MRI (magnetic resonance imaging). For participants who died during the study period without a previous diagnosis of dementia or CIND, dementia diagnoses were also ascertained from death certificates based on the following causes of death listed anywhere on the death certificate: dementia in Alzheimer's disease, vascular dementia, other dementia, or unspecified dementia. For this analysis, dementia and CIND were combined into one outcome, dementia/CIND.

Mortality

Mortality ascertainment included interviews with family members to track participants who could not be reached for annual study visits or interim six month phone calls, online surveillance of

death notices, review of the Social Security Death Index, the National Death Index, and vital statistics data files from the state of California. Mortality surveillance is ongoing, but this analysis is limited to deaths that occurred during active follow-up for dementia/CIND (1998-2007). We had complete or partial social security numbers on most (80%) of deceased and obtained death certificates and cause of death for 93.1% of deceased participants. We classified cause of death using *International Classification of Diseases, Tenth Revision*.

Other variables

At the baseline interview, participants reported their age, sex, years of education, country of birth, whether or not they had a regular medical doctor (as a marker of access to medical care), smoking status, and any alcohol use. As a marker of physical activity, participants were asked to classify their usual outdoor walking pace as never walks outdoors/unable to walk, easy pace, brisk pace. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale (CESD), a widely used scale (range 0-60) [30]. Fasting blood samples were taken at annual study visits. Fasting glucose was measured with the Cobas Mira Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Fasting insulin was measured using a double-antibody radioimmunoassay using ^{125}I human insulin tracer (Linco Research, St. Charles, MO), a guinea pig anti-porcine insulin first antibody (Michigan Diabetes Research and Training Center, Ann Arbor, MI), and a goat anti-guinea pig gamma globulin (Antibodies Incorporated, Davis, CA) and standardized against the Human Insulin International Reference Preparation for Insulin. Sitting systolic and diastolic blood pressure measurements were taken with an automatic digital blood pressure monitor twice at a ten minute interval and averaged. Hypertension was based on measured systolic blood pressure (≥140mmHg), self-report of a physician diagnosis, and/or anti-hypertensive medication use. Waist circumference was measured at the level of the umbilicus at mid-respiration with the participant standing erect. History of stroke was based on self-report of a physician diagnosis and hospitalization.

Statistical analysis

The objective of the analysis was to examine the association of diabetes with incidence of dementia/CIND and to account for the competing risk of mortality. We first compared baseline descriptive characteristics by treated and untreated diabetes status (ever vs. never during study) with ANOVA for continuous variables and chi-square tests for categorical variables.

We evaluated the association of treated and untreated diabetes with incidence of dementia/CIND using competing risk regression models with the method proposed by Fine and Gray [31]. Participants were observed from study entry until the occurrence of dementia/CIND (the event of interest), death (the competing event), or censoring (last date of contact). We used time-dependent diabetes as the exposure variable for all models to capture all diabetes cases that occurred prior to diagnosis of dementia, death, or censoring and time-dependent variables for covariates to reflect changes in values throughout the study period. Because of the strong association between dementia and age, for all models, we used age at diagnosis, death, or censoring as the time-scale and adjusted for baseline age [32].

Our competing risk regression approach accounts for the fact that individuals who die prior to developing dementia/CIND will never develop dementia/CIND. Thus, the association between diabetes and dementia/CIND depends on the association between diabetes and death [33-35]. Like the standard Cox regression model, this approach measures the association of diabetes with risk of dementia/CIND with a hazard ratio (HR). Since previous studies of this issue have not accounted for the competing risk of death, we also specified Cox regression models, where participants who died were censored at age at death, to examine how taking into account the competing risk of death influenced risk estimates.

We examined the influence of covariates on the association of diabetes (time-dependent) with risk of dementia/CIND with a series of models. We evaluated whether dementia/CIND incidence differed among those with diabetes who were taking anti-diabetic medications from those with diabetes who

were not taking anti-diabetic medications using a three-level exposure variable (no diabetes, untreated diabetes, treated diabetes). Model 1 was adjusted for age (as time-scale), sex, and years of education. Model 2 further adjusted for waist circumference (time-dependent) to control for central obesity as a potential confounder. Model 3 (fully-adjusted model) added adjustment for (time-dependent) stroke to Model 2 to account for stroke as a potential intermediary variable between diabetes and dementia/CIND. We assessed whether stroke modified the effect of diabetes on dementia/CIND risk by adding a multiplicative interaction term between stroke and diabetes to Model 3. In analyses not reported here, we adjusted for hypertension, depressive symptoms, alcohol use, smoking status, outdoor walking pace, and having a regular medical doctor as potential confounders, but did not include these variables in the final models because they did not substantially (e.g. ≥10%) alter the magnitude of the HRs for diabetes. We graphically displayed the estimated cumulative incidence of dementia/CIND by diabetes status from the fully-adjusted competing risk regression model (Figure 1.2).

We separately evaluated the association between dementia/CIND or diabetes and death with Cox regression models adjusted for the same covariates included in the models of the association of diabetes with risk of dementia/CIND described above. Summary statistics were run using SAS 9.2 (SAS Institute Inc, Cary, NC). All regression models were run in Stata 11 (StataCorp, College Station, TX). Competing risk regression models were estimated using Stata command stcrreg, and cumulative incidence curves were estimated using Stata command stcurve with option cif.

Results

Figure 1.1 shows the flow of study participants throughout the study. A total of 1,789 adults ≥60 years of age were enrolled in SALSA in 1998-99. A total of 172 participants were excluded from this analysis: 115 had dementia/CIND at the baseline visit and 57 did not participate in any follow-up visits. The resulting sample size was 1,617 participants at risk for dementia/CIND. Out of the 1,617

participants, 677 (41.9%) had diabetes during the study (n=513 baseline diabetes cases, n=164 incident diabetes cases). The majority (77%) of participants with diabetes were using anti-diabetic medications. There were 159 incident dementia/CIND cases. A total of 24 (15.1%) of the dementia/CIND cases were ascertained only from death certificates. Of those, 83.3% (n=20) had a cognitive test score below the cut-point for dementia assessment. A total of 298 participants died during the study period without a diagnosis of dementia/CIND. The remaining 1,160 participants were censored at the age of last contact with the study. In addition to the deaths that occurred among participants without dementia/CIND, 63 participants with dementia/CIND died during the study period, for a total of 361 deaths. Average non-mortality annual attrition due to refusals and loss to follow-up was 2.9% per year. The mean follow-up time was 6.5 years (SD 2.5 years).

Table 1 shows the baseline characteristics of the sample by treated and untreated diabetes status (ever vs. never) in the at-risk sample. On average, compared to those without diabetes, participants with diabetes were slightly younger, more likely to be born in the United States, and to have a regular medical doctor, which may reflect better access to health care among those with diabetes. Years of education did not differ by diabetes status. They were less likely to be current smokers but more likely to have a history of smoking. They were more likely to have hypertension, larger waist circumferences, higher fasting glucose and insulin, and a history of stroke, myocardial infarction, intermittent claudication, and kidney disease.

Compared to those with treated diabetes, those with untreated diabetes were more often immigrants, had smaller waists, lower glucose and insulin, less hypertension, and fewer reports of stroke, myocardial infarction, congestive heart failure, intermittent claudication, and kidney disease.

Among participants with diabetes, 62.2% met at least two criteria for diabetes in this study (elevated fasting glucose, anti-diabetic medication use, or self-report) and 37.8% met one (13.3% fasting glucose, 3.4% anti-diabetic medication use, or 21.1% self-report) (data not shown in tables). Among the

participants who reported a physician diagnosis of diabetes at baseline, the median reported duration of diabetes was 10 years (interquartile range 5-20 years). At baseline, 64.7% of participants with diabetes were using anti-diabetic medications: 36.1% were using one medication and 28.7% were using two or more medications. Sulfonylureas were the most common class (73%) of anti-diabetic drugs [36]. The proportion of patients taking anti-diabetic medications remained relatively constant throughout follow-up (64.7% in year 1 up to 69% in year 7).

More participants with diabetes died (n=182, 26.9%) than participants without diabetes (n=179, 19.0%). In a Cox model, treated and untreated diabetes were associated with increased risk of death after adjustment for sex, education, time-dependent waist circumference, and time-dependent stroke (HR=2.15, 95% CI: 1.58-2.95, HR=2.12, 95% CI: 1.65-2.73). There were more deaths among participants with incident dementia/CIND (n=63, 39.6%) than among those without dementia/CIND (n=298, 20.4%). Incident dementia/CIND was associated with an increased risk of death in a Cox model adjusted for the same covariates (HR=2.48, 95% CI: 1.75-3.51).

Table 2 shows the HRs relating time-dependent diabetes to the incidence of dementia/CIND from competing risk models and Cox models. In both types of models, treated diabetes was associated with higher incidence of dementia/CIND than no diabetes. Untreated diabetes was only associated with higher incidence of dementia/CIND in Cox models. Comparison of dementia/CIND risk in treated to untreated diabetes was not significant (HR=1.32, 95% CI: (0.80-2.19), p=0.28). In Model 2, adjustment for time-dependent waist circumference, a potential confounder of the association between diabetes and dementia/CIND risk, increased the HRs for treated diabetes and untreated diabetes by 10% and 15%, respectively, compared to the base model (Model 1) that adjusted for only age (as time-scale), sex, and years of education. In Model 3 (fully-adjusted model), addition of time-dependent stroke modestly decreased the HR for treated diabetes by 9% and untreated diabetes by 10%, but the association with treated diabetes remained strong and statistically significant. Time-dependent stroke did not modify the

association between diabetes and dementia/CIND (interaction between stroke and diabetes p=0.97, data not shown). Compared to the Cox regression Model 3, accounting for competing risk of death in Model 3, attenuated the HR for treated diabetes by 14% and for untreated diabetes by 18%.

Figure 1.2 displays the estimated cumulative incidence functions for dementia/CIND among by diabetes status from the fully-adjusted competing risk regression model (Model 3). The graph demonstrates that the incidence of dementia/CIND was highest among those with treated diabetes, followed by people untreated for diabetes and then those without diabetes.

Discussion

In this ten-year population-based study, we found that those with treated diabetes had a two-fold increased risk of dementia/CIND among older Mexican Americans, even after accounting for the competing risk of mortality and changes over time in risk factor exposures. Those with treated diabetes in our sample have higher glucose and insulin, hypertension, more co-morbid cardiovascular disease and may have more severe diabetes than those who were untreated. This may explain why their dementia risk is higher, given that the risk of death is similar in both groups. However, comparison of dementia/CIND risk in treated to untreated diabetes was not statistically significant (HR treated vs. untreated: 1.32, p=0.28). Standard Cox models that do not incorporate adjustment for competing risk consistently provided a larger estimate of effect.

Previous epidemiologic studies in non-Hispanic white populations have also found that diabetes is associated with a two-fold increased risk of dementia [2-13]. Most research on the association between diabetes and dementia has been conducted in non-Hispanic white populations, where diabetes burden is lower than among Mexican Americans [16]. To our knowledge, this is the first study to evaluate the association between diabetes and dementia or CIND among older Mexican Americans.

In addition to studying a different ethnic group, the present study differs from previous studies because the analysis takes into account the competing risk of death. It is well established that diabetes is associated with higher mortality rates [16], and previous studies have also shown that cognitive decline [22, 23] is associated with an increased risk of death. Diabetes-related mortality differentially influences the number of dementia/CIND cases that occur. Since diabetes is associated with death, a standard Cox model, which ignores the competing risk of death, may result in an overestimation of the effect of diabetes on incidence of dementia/CIND [34, 37]. While the Cox model treats deaths as censored observations and removes individuals from the denominator for the hazard rate at death, the competing risk model treats death as a competing risk by retaining those who die without dementia in the denominator for the hazard rate. In effect, this approach models these individuals as no longer at risk for dementia/CIND. This results in a lower HR than the standard Cox model. The competing risk regression model produces estimates that reflect the actual incidence of dementia/CIND among people with diabetes compared to those without diabetes. This approach may be useful for clinical predictions and for predictions of future dementia/CIND incidence in the population. In this population, accounting for the competing risk of death altered the fully-adjusted risk estimates for treated and untreated diabetes by 14% and 18%, respectively. This change is large enough (≥10%) to be considered an important confounder by conventional confounder identification criteria [38].

These findings have important implications for prediction of future dementia incidence among Mexican Americans and in other racial/ethnic groups. It is important to consider how future changes in mortality rates among people with diabetes may affect dementia rates. A recent publication from the National Health Interview Survey (NHIS) reported that mortality rates among adults with diabetes declined by 23% between 1997 and 2006 [20]. This trend was observed in the overall population, as well as across age and racial/ethnic subgroups; the decline was greatest among Hispanics (38%). The authors point out the change in death rates is likely due to multiple factors, including improved diabetes medical

care, treatments, and self-management behaviors. In fact, results from NHANES 1999-2008[39] suggest that blood pressure, glycemic control, LDL-C and HBA1c have improved in Mexican Americans as well as other groups. These improvements may propel the decline in mortality rates observed over the same period. These changes have important public health implications for future incidence of dementia/CIND in the population. The potential impact on dementia/CIND incidence among people with diabetes will depend on the factors causing the decline in the mortality rate. If mortality rates among those with diabetes decline due to earlier screening and improved management and therefore decreases in disease progression and severity, dementia/CIND rates among people with diabetes might also decrease. If mortality rates decline among those with diabetes without reducing disease severity, and, if more severe diabetes influences dementia risk, dementia/CIND rates among people with diabetes could potentially increase.

SALSA is a population-based study. The sample is representative of older Latinos residing in the Sacramento Area in California in 1998-99 [24]. The risk estimates from this study are generalizable to populations with similar characteristics, including similar mortality rates. In this population, diabetes was associated with over a two-fold increased risk of death. Mortality associated with diabetes is slightly higher in our population than in two recent nationally-representative studies: the NHIS [20] and the Cancer Prevention Study-II [21]. In both of these studies, diabetes was associated with a nearly two-fold increased risk of death.

A major strength of this study is the large sample and population-based longitudinal design, which enabled us to study incident dementia/CIND over a long time period in an understudied ethnic group with a high burden of diabetes. This is the only population-based study of clinically assessed dementia in Mexican Americans. Because our analysis accounted for the competing risk of death, our results can be interpreted as the absolute risk of dementia/CIND among people with diabetes compared to those without, making our results relevant for clinical decision making and public health predictions.

This study also has some limitations. As for any study of older adults, individuals had to survive at least to age 60 to participate in this study. Selection due to premature mortality among people with diabetes before age 60 may have occurred and affected the risk estimate in our sample. Mortality was the primary source of attrition, but some non-mortality attrition was present. Participants with diabetes and participants experiencing symptoms of dementia/CIND may have been more likely to drop out of the study than healthier participants, which could have biased our results towards the null. Stroke was measured by self-report of a physician diagnosis which is likely to underestimate the presence of strokes, especially 'silent strokes'. This would tend to attenuate the association between stroke and dementia because undiagnosed strokes are included in the 'non-stroke' category. To the extent to which stroke is on the pathway between diabetes and dementia, such misclassification may reduce the influence of adjustment for stroke on that association. Physical activity was estimated by self-reported outdoor walking speed, which may underestimate physical activity levels. As in all observational studies, we cannot rule out the possibility of residual confounding, particularly from unmeasured behavioral factors.

In conclusion, we found that treated type 2 diabetes is associated with a two-fold increased incidence of dementia/CIND in older Mexican Americans, even after accounting for the competing risk of mortality. Screening and treatment for diabetes that changes survival among those with type 2 diabetes may influence future dementia incidence rates. Cognitive screening in those with diabetes is warranted by the preponderance of evidence supporting a robust link between diabetes and dementia.

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Table 1.1. Baseline characteristics of participants by diabetes status (ever vs. never) during study (n=1617).

Variable	Diabetes treated	Diabetes untreated	No diabetes	*p-value*
Age (years)	69.6 (6.4)	69.7 (6.3)	70.7 (7.1)	0.010
Male sex	44.4	47.1	40.1	0.117
Education (years)	7.4 (5.4)	7.4 (5.5)	7.4 (5.3)	0.99
U.S. born	55.8	49.7	46.3	0.0025
Regular medical doctor	91.3	88.4	86.9	0.040
Health insurance	92.7	89.0	90.0	0.17
Smoking status				0.0013
Never smoked	41.7	45.2	48.0	
Former smoker	48.7	47.7	38.8	
Current smoker	9.6	7.1	13.2	
Waist circumference (inches) >40 male, 35 female	63.8	47.1	40.5	<0.001
Fasting glucose (mg/dL)	151.8 (57.8)	119.3 (40.5)	92.1 (11.0)	<0.001
Fasting glucose ≥126 mg/dL	58.8	23.2	0	<0.001
Fasting insulin (µIU/mL)	13.8 (13.4)	13.1 (10.8)	10.5 (20.8)	0.0025
Hypertension	73.0	67.7	57.1	<0.001
Stroke	11.4	6.5	6.2	0.0019
Myocardial infarction	12.5	9.7	5.6	<0.001
Congestive heart failure	3.9	3.9	1.7	0.030
Intermittent claudication	12.1	7.9	6.3	<0.001
Kidney disease	13.9	7.8	5.5	<0.001

Continuous variables are displayed as mean (SD), categorical variables are displayed as column %. *P* values comparing characteristics between those with and those without diabetes are two-sided.

Table 1.2. Hazard ratios from competing risk regression models relating diabetes and incidence of dementia/CIND.

	Competing Risk models	Cox Models
Model	HR (95% CI)	HR (95% CI)
Model 1		
No diabetes (ref)	1.0	1.0
Diabetes untreated	1.50 (0.94, 2.40)	1.93 (1.22, 3.07)
Diabetes treated	2.06 (1.47, 2.91)	2.38 (1.68, 3.37)
Female vs. male sex	1.35 (0.98, 1.86)	1.22 (0.88, 1.68)
Education (years)	0.96 (0.93, 0.99)	0.97 (0.94,1.00)
Model 2		
No diabetes (ref)	1.0	1.0
Diabetes untreated	1.73 (1.05, 2.86)	2.16 (1.33, 3.54)
Diabetes treated	2.26 (1.57, 3.27)	2.66 (1.85, 3.83)
Female vs. male sex	1.31 (0.93, 1.83)	1.14 (0.81, 1.61)
Education (years)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)
Waist circumference (inches) (TD)	0.97 (0.94, 1.00)	0.96 (0.93, 1.00)
Model 3		
No diabetes (ref)	1.0	1.0
Diabetes untreated	1.55 (0.93, 2.58)	1.88 (1.15, 3.07)
Diabetes treated	2.05 (1.41, 2.97)	2.38 (1.65, 3.44)
Female vs. male sex	1.30 (0.92, 1.82)	1.15 (0.82, 1.61)
Education (years)	0.95 (0.92, 0.99)	0.96 (0.93, 0.99)
Waist circumference (inches) (TD)	0.97 (0.94, 1.00)	0.97 (0.93, 1.00)
Stroke (TD)	2.95 (2.04, 4.27)	3.28 (2.28, 4.72)

TD = “time-dependent.” Age adjusted for entry-age is the time-scale in all models.

Figure 1.1. Flow of study participants, Sacramento Area Latino Study on Aging, 1998-2007.

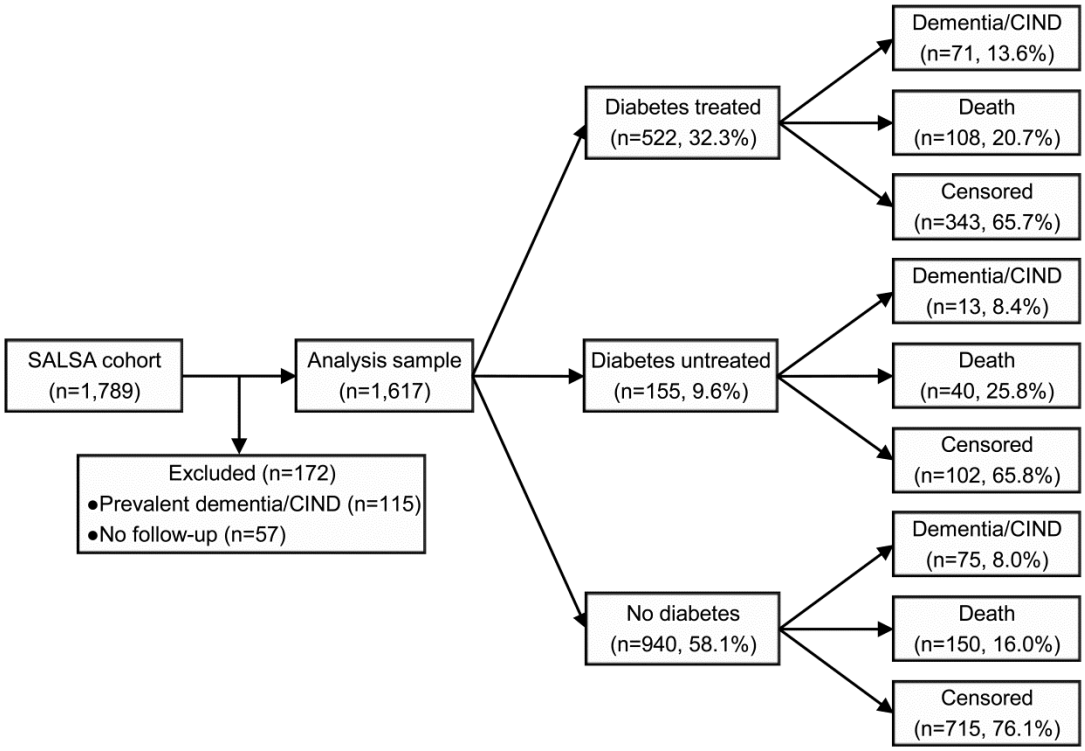
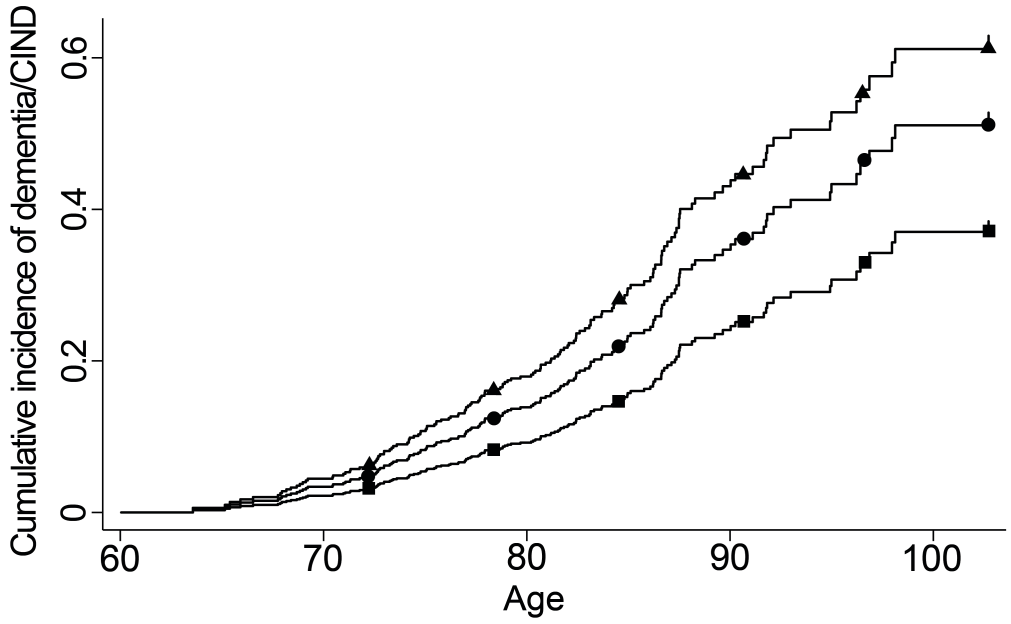


Figure 1.2. Cumulative incidence functions for dementia/CIND by diabetes status, accounting for the competing risk of death, from competing risk regression model adjusted for sex, years of education, waist circumference, and stroke.



Squares = no diabetes, circles = diabetes untreated, triangles = diabetes treated.

Chapter 2: Type 2 diabetes, 10-year cognitive decline, and risk of death among older Mexican Americans

Introduction

The prevalence of type 2 diabetes has increased dramatically in the U.S. over the past two decades (1) and is particularly high among older adults (2). In addition to being at risk for well-established diabetes-related complications, older adults with diabetes may also experience accelerated cognitive decline. Identifying causes of early cognitive decline is essential for prevention and early intervention, which are likely to be most effective in preventing or slowing progression to dementia. Due to the high prevalence of type 2 diabetes and the growing population of older adults in the U.S. (3), even a modest effect of diabetes on cognitive decline could have a substantial public health impact. The prevalence of type 2 diabetes is particularly high among Mexican Americans (2), and Mexican Americans with diabetes tend to have poorer glycemic control than other racial/ethnic groups (4). However, the association between diabetes and cognitive decline has not been thoroughly examined in this growing ethnic group.

Examining cognitive change over time in older adults is complicated by high mortality rates. In longitudinal studies of older adults, death leads to substantial attrition to study cohorts over time that may alter observed associations between risk factors and outcomes. In standard statistical models, death is treated as a form of non-informative censoring, and models are based on the assumption that death is not associated with the outcome of interest. However, many health conditions, including type 2 diabetes (5), are associated with a higher mortality rates, and accelerated cognitive decline is observed in years prior to death among older adults (6-8). Earlier death among people with type 2 diabetes compared to those without may influence the observed association between diabetes and cognitive decline because those who die earlier likely experience greater cognitive decline, but contribute to less

follow-up, than those who live longer. As a result, earlier death among people with diabetes could change the observed association between diabetes and cognitive decline. Although the importance of accounting for the potential influence of death on observed risk factor-disease associations in longitudinal studies of older adults has been discussed (9), available methods have not been widely applied in practice, and prior studies examining the association between type 2 diabetes and cognitive decline have not accounted for death.

The objective of this paper is to evaluate the effect of type 2 diabetes on cognitive decline over ten years while accounting for the influence of death in a cohort of older Mexican Americans with a high prevalence of diabetes who were free of dementia at baseline.

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 participant language of preference. A detailed description of study procedures has been published previously (10). 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 each 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 each study visit, 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 (61%) of participants with diabetes met at least two criteria and 39% met one (13% fasting glucose level, 4% medication use, and 22% self-report). Due to the advanced age of the cohort, most diabetes cases are likely to be type 2 diabetes. Throughout this paper, we will use the term "diabetes" to refer to type 2 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 (11). Scores on the 3MSE range from 0-100, where higher test scores indicate better cognitive function. The distribution of 3MSE scores was left-skewered. To correspond more closely to a normal distribution, we examined the log-transformation of the errors on the 3MSE [log(101 – 3MSE score)]. More errors indicate poorer cognitive function, and an increase in log(3MSE errors) over time indicates cognitive decline.

Death. Mortality ascertainment included 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. Age, sex, years of formal education, country of birth, and smoking were collected from a structured baseline interview. History of vascular disease, including history of stroke, myocardial infarction, congestive heart failure, and intermittent claudication, was collected from the

baseline interview and updated at every study examination. Waist circumference, body mass index (BMI), and blood pressure were measured at every study examination. 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) (12). BMI was calculated from direct measurements of height and weight. Blood pressure was measured while the participant was sitting by taking the average of two blood pressure measurements taken on the left arm five minutes apart.

Statistical analysis

We first compared baseline characteristics of the sample by diabetes status (ever vs. never during the study period) with *t*-tests for continuous variables and chi-square tests for categorical variables.

To examine the association between time-dependent diabetes and change in cognitive function while accounting for the dependence between cognitive decline and death, we used a joint longitudinal-survival model (13) to simultaneously model cognitive decline and risk of death. This modeling approach accommodates the dependence between cognitive decline and death by adjusting for participants who die earlier in the study period. The joint model was comprised of two sub-models that use a shared parameter for rate of cognitive change (random effect for linear slope): a sub-model for repeated measures of cognitive function (linear mixed effects model (14)) and a sub-model for time to death (piecewise exponential model (15)). The linear mixed effects sub-model included random effects for intercept and linear slope. We included a quadratic term for time to account for a curvilinear trajectory of cognitive function. We estimated the difference in average annual rate of change in cognitive function associated with diabetes with interaction terms between time-dependent diabetes and time (diabetes*time and diabetes*time^2). For the piecewise exponential sub-model, we divided the time-scale into five two-year intervals. Both sub-models used time from enrollment (in years) as the time-

scale and included time-dependent covariates to account for changes in exposures over time. Joint models were run using PROC NLMIXED following the approach described by Guo and Carlin (16). A detailed description of the joint model specifications and considerations is included in the Supplementary Appendix.

We fit a series of models to assess the association between diabetes and cognitive decline while accounting for death. First, we fit a model with time-dependent 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, time-dependent stroke, and time-dependent diastolic blood pressure (Model 3). We considered adjusting for time-dependent systolic blood pressure, but did not include it in the final model because inclusion only changed the interaction between diabetes and time by 1%. We illustrated predicted cognitive change among those with diabetes and those without from Model 3 in Figure 2.1. For ease of interpretation, all continuous variables were centered at the mean baseline value for the study sample.

We further examined cognitive trajectories among participants who died during the study and among those who did not die during the study with mixed linear effects models stratified by death status (died during the study period vs. censored). We illustrated predicted cognitive change by diabetes and death status in Figure 2.2.

At baseline, 5.9% of participants were missing data on covariates included in this analysis. 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 (17). Five imputed datasets were created using Imputation and Variance Estimation Software (18). The results from regression analyses from the five imputed datasets were summarized using the MI ANALYZE procedure.

All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Participants were followed from enrollment in 1998-1999 through 2007. A total of 1,789 participants were 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 for this analysis was 1,634 individuals.

The median follow-up time was 7.6 years (interquartile range: 4.8-8.2). A total of 788 (48.2%) of the 1634 participants had diabetes: 530 (67.3%) had diabetes at baseline and 258 (32.7%) were incident cases. Among participants with diabetes at baseline, 35.9% were using an anti-diabetic medication, and the proportion of participants with diabetes using an anti-diabetic medication ranged from 30-40% throughout the study. Throughout the study, there were 372 (22.8%) deaths. Nearly 25% of participants with diabetes died compared to 20.8% of participants without diabetes (p=0.05).

At baseline, participants with diabetes were slightly younger, more likely to be born in the U.S., more likely to be a former smoker, have abdominal obesity, higher BMIs and systolic blood pressures, and a higher prevalence of history of stroke, myocardial infarction, congestive heart failure, and intermittent claudication (Table 2.1).

From joint longitudinal-survival models, those with diabetes experienced more cognitive decline compared to those without diabetes and both time-dependent diabetes and cognitive decline (increase in log(3MSE errors)) were associated with an increased risk of death (Table 2.2). Adjustment for potential confounders modestly altered estimates of cognitive change. The fully-adjusted association between diabetes and change in 3MSE scores over time are illustrated in Figure 2.1. The 3MSE scores for both participants with and without diabetes increased through year 4, although scores increased less among participants with diabetes, and declined thereafter. Results from a separate linear mixed effects model for time-dependent diabetes and cognitive decline (Supplementary Appendix Table 2.3S) were similar to results from the joint model.

Figure 2.2 illustrates the trajectories of change in 3MSE scores by diabetes status among participants who died and those who did not die during the study period (censored). Although the interaction terms between death and time were non-significant (death*time p=0.19, death*time^2 p=0.84), the observed trend was the trajectory of cognitive decline among participants who died was accelerated compared to those who did not die during the study period, regardless of diabetes status.

Discussion

In this cohort of older Mexican Americans without dementia at baseline, diabetes contributed to accelerated cognitive decline over a 10 year period. Although both diabetes and cognitive decline were associated with an increased risk of death, adjusting for the dependence between cognitive decline and death with joint models did not substantially impact the estimated association between diabetes and cognitive decline.

We observed an inverted "U" shaped curvilinear change in cognitive function over time, which may reflect a positive learning effect. Prior studies have observed learning effects on cognitive tests administered a year or more apart among older adults without dementia (8, 19-21). The ability to retain a learning strategy for a test taken at 12-15 month intervals may represent better cognitive function. The positive learning effect was not present among those who died, perhaps reflecting more severe initial impairment.

The differences in change in 3MSE scores over the study period between participants with diabetes and without diabetes were modest. The largest difference in cognitive test scores was at years 5 and 6, when the observed difference between groups was only 1.2 points on the 3MSE. However, due to the high prevalence of diabetes, even a small impact on cognitive decline could have a substantial public health impact. Furthermore, the impact of diabetes on cognitive decline likely varies among people with diabetes, and may be greater among individuals with more advanced disease.

Previously, we found that diabetes is associated with a two-fold increased incidence of cognitive impairment and dementia in this same population (22). In the present study, we found a modest association between diabetes and cognitive decline. All participants free of dementia at baseline, including those who did not experience cognitive decline and those who developed incident dementia during the study, contributed to trajectories of cognitive function. Cognitive decline can impact quality of life prior to progression to dementia, and identifying risk factors for early cognitive decline is valuable for identifying prevention strategies and early interventions, which are likely to have the greatest impact on preventing or delaying dementia.

Several previous studies examining the association between diabetes and cognitive decline in non-Hispanic white and African American populations have found that diabetes is associated with greater cognitive decline among older adults (23-28), although a few studies have reported no association (29, 30). The inconsistent results may be in part due to the length of study, the cognitive domains assessed, the specific neuropsychological tests used, and how change in cognitive function was modeled. The association between diabetes and cognitive decline over two years has been previously 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), but that study was limited to two sequential cognitive assessments. The authors found that self-reported diabetes was associated with a higher risk of severe cognitive impairment but not moderate impairment.

Our study has numerous important strengths. SALSA is a population-based study, and participants were representative of community-dwelling older Mexican Americans living in the Sacramento Area in 1998-1999 (10). Study interviews and the 3MSE were validated in both English and Spanish. The results of this study are generalizable to community-dwelling older Mexican Americans, as

well as other populations with similar risk factors and mortality rates. This prospective, longitudinal design includes repeated measures of cognitive assessment. Our analysis accounted for the dependence between cognitive decline and death by adjusting for participants who died earlier in the study period. To our knowledge, this is the first population-based study to examine the association between diabetes and cognitive decline with repeated cognitive assessments among Mexican Americans.

This study has some 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 association between diabetes and cognitive decline. The 3MSE is a test of global cognitive function, so inferences about the effects of diabetes on other cognitive domains cannot be drawn from this study.

Among older Mexican Americans, those with diabetes experienced modestly greater cognitive decline and higher mortality rates than those without diabetes. Future studies should investigate how diabetes treatments and resultant changes in diabetes-related mortality impact cognitive decline among older adults with diabetes.

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Table 2.1. Baseline characteristics of the sample by diabetes status (ever/never).

Variable	Categories	No diabetes (n=846)	Diabetes (n=788)	*p*-value
		Mean (SD) or n (%)	Mean (SD) or n (%)	
Age (years)		70.95 (7.08)	69.60 (6.38)	<0.001
Sex	Male Female	341 (40.31) 505 (59.69)	348 (44.16) 440 (55.84)	0.11
Country of birth	U.S. Mexico	403 (47.64) 443 (52.36)	415 (52.66) 373 (47.34)	0.042
Education (years)		7.57 (5.26)	7.27 (5.39)	0.26
Smoking status	Never smoked Former smoker Current smoker	411 (48.58) 325 (38.42) 110 (13.00)	335 (42.51) 379 (48.10) 74 (9.39)	<0.001
Waist circumference (inches) >40 male, >35 female	Yes	369 (43.62)	476 (60.41)	<0.001
BMI category (kg/m^2)	<25 25-30 ≥30	212 (25.06) 318 (37.59) 316 (37.35)	103 (13.07) 298 (37.82) 387 (49.11)	<0.001
Fasting blood glucose (mg/dL)		91.8 (11.0)	138.1 (55.4)	<0.001
Systolic blood pressure (mmHg)		137.59 (19.10)	139.59 (18.77)	0.033
Diastolic blood pressure (mmHg)		75.97 (10.18)	75.82 (11.00)	0.78
Stroke	Yes	64 (7.23)	100 (11.98)	<0.001
Myocardial infarction	Yes	49 (5.79)	91 (11.55)	<0.001
Congestive heart failure	Yes	17 (2.01)	30 (3.81)	0.030
Intermittent claudication	Yes	54 (6.38)	82 (10.41)	0.003

t-tests were used for continuous variables, chi-square tests were used for categorical variables; p-values are two-sided.

Table 2.2.Regression coefficients (b) to describe the association between time-dependent diabetes and change in cognitive function (log(3MSE errors)), and hazard ratios (HR) to describe the association between time-dependent diabetes and cognitive decline and risk of death from joint longitudinal-survival models.

	Model 1				Model 2				Model 3			
	AIC: 23664				AIC: 22645				AIC: 22610			
Longitudinal sub-model												
Parameter	b	95% CI		*p*-value	b	95% CI		*p*-value	b	95% CI		*p*-value
Intercept	2.427	2.378	2.475	<0.001	2.411	2.359	2.464	<0.001	2.401	2.343	2.458	<0.001
Time (years)	-0.143	-0.167	-0.119	<0.001	-0.144	-0.168	-0.120	<0.001	-0.148	-0.172	-0.124	<0.001
$Time^2$	0.019	0.015	0.022	<0.001	0.018	0.015	0.021	<0.001	0.018	0.015	0.021	<0.001
Diabetes (TD)	0.012	-0.065	0.089	0.750	0.042	-0.027	0.112	0.230	0.042	-0.028	0.111	0.240
Diabetes*Time	0.043	0.001	0.085	0.043	0.043	0.002	0.085	0.041	0.039	-0.003	0.080	0.067
Diabetes*$Time^2$	-0.004	-0.010	0.001	0.088	-0.005	-0.010	0.001	0.079	-0.004	-0.009	0.001	0.120
Age (baseline, years)	-	-	-	-	0.024	0.019	0.028	<0.001	0.024	0.019	0.028	<0.001
Female sex	-	-	-	-	0.016	-0.036	0.068	0.550	0.024	-0.028	0.077	0.360
Education (years)	-	-	-	-	-0.076	-0.081	-0.071	<0.001	-0.076	-0.081	-0.071	<0.001
Large waist (baseline)	-	-	-	-	-	-	-	-	-0.014	-0.070	0.041	0.61
Stroke (TD)	-	-	-	-	-	-	-	-	0.185	0.100	0.270	<0.001
Diastolic blood pressure (TD, 10 mmHg)	-	-	-	-	-	-	-	-	0.028	0.010	0.046	0.0036
Survival sub-model												
Parameter	HR	95% CI		*p*-value	HR	95% CI		*p*-value	HR	95% CI		*p*-value
Diabetes (TD)	1.41	1.11	1.79	<0.001	1.56	1.25	1.94	<0.001	1.49	1.19	1.87	<0.001
log(3MSE errors) slope (1 SD unit*)	2.73	2.09	3.57	<0.001	1.57	1.30	1.91	<0.001	1.51	1.24	1.84	<0.001

TD=time-dependent; SD=standard deviation. Age, education, and diastolic blood pressure are centered at mean baseline values.
Model 1: unadjusted; Model 2: adjusted for age, sex, and education; Model 3: Model 2 + large waist circumference, stroke, diastolic blood pressure.

Figure 2.1. Predicted 3MSE scores from the joint longitudinal-survival model to describe the association between time-dependent diabetes and change in cognitive function. Predictions are for a male individual 70 years of age with 7 years of education, waist circumference <40 inches, no history of stroke, and diastolic blood pressure 76 mmHg.

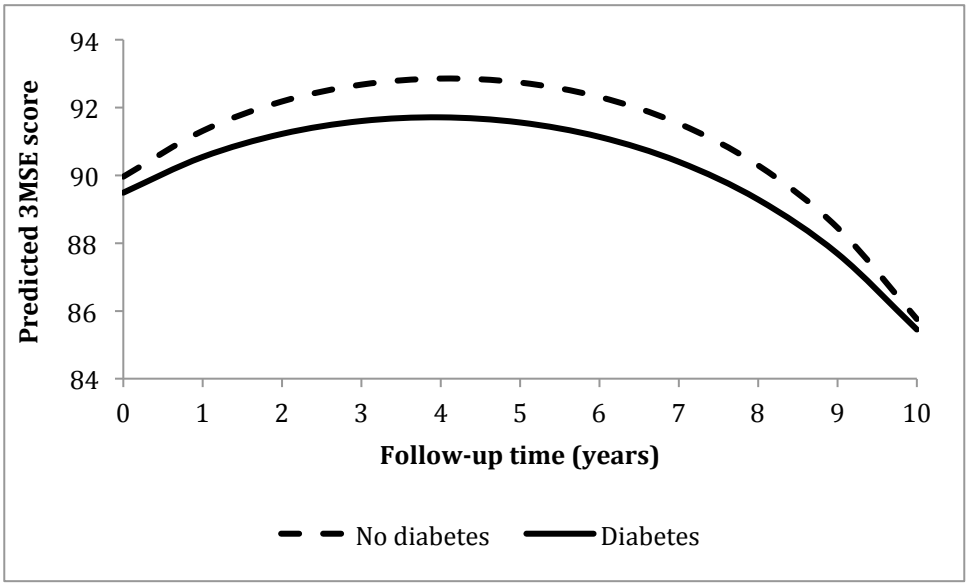
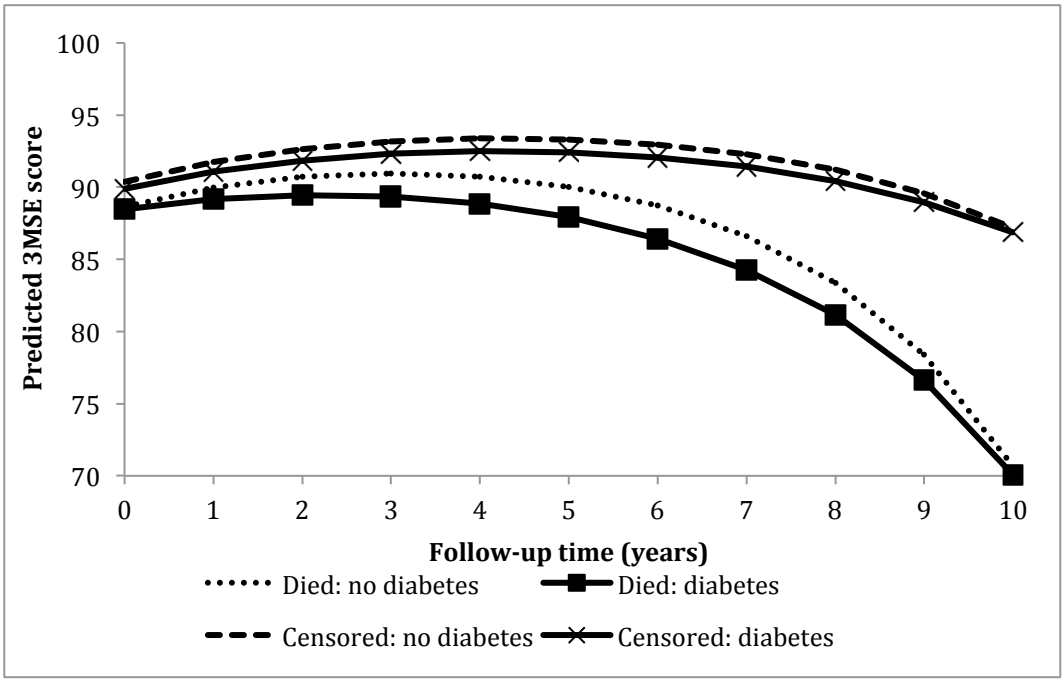


Figure 2.2. Predicted 3MSE scores from the mixed linear effects model to describe the association between time-dependent diabetes and change in cognitive function by survival status. Predictions are for a male individual 70 years of age with 7 years of education, waist circumference <40 inches, no history of stroke, and diastolic blood pressure 76 mmHg.



Supplementary Appendix

Statistical Analysis

To examine the association between time-dependent diabetes and change in cognitive function while accounting for the dependence between cognitive decline and death, we used a joint longitudinal-survival model (13) to simultaneously model cognitive decline and risk of death. This modeling approach accommodates the dependence between cognitive decline and death by adjusting for participants who die earlier in the study period. The joint model was comprised of two sub-models that use a shared parameter for rate of cognitive change (random effect for linear slope): a sub-model for repeated measures of cognitive function (linear mixed effects model (14)) and a sub-model for time to death (piecewise exponential model (15)). In addition to including a shared parameter for slope, we considered including a shared parameter for intercept, but excluded it from final models because the parameters were highly correlated and including both terms led to inflated standard errors for the shared parameters, but had little impact on other model parameters. Both sub-models used time from enrollment (in years) as the time-scale and included time-dependent covariates to account for changes in exposures over time. Joint models were run using PROC NLMIXED in SAS version 9.2 (SAS Institute, Cary, North Carolina) following the approach described by Guo and Carlin (16).

The linear mixed effects sub-model modeled the association between diabetes and change in cognitive function over time (as log(3MSE errors)). The trajectory of log(3MSE errors) over time was curvilinear, so we included a quadratic term for time, which improved the model fit (Likelihood Ratio Test, $p < 0.001$). We included random effects for intercept and linear slope. Quadratic slope was not included as a random effect because when included, the variance parameter was estimated to be zero. The models included two-way interaction terms between time-dependent diabetes and time (diabetes*time and diabetes*time^2) to estimate the difference in average annual rate of change in

cognitive function associated with diabetes. In addition to fitting a joint model, we examined the association between time-dependent diabetes and cognitive decline with a separate mixed linear effects model.

We used a piecewise exponential model for the survival sub-model since the model described the data well, allowing the hazard function to change over time and the model allowed time-dependent covariates. In addition, we could implement this sub-model in the joint longitudinal-survival model using standard statistical software. We divided the time scale into five two-year intervals since this division corresponded reasonably well with the spacing of the cognitive assessments and the hazard function appeared relatively constant within each two-year interval.

Table 2.3S. Regression coefficients (b) to describe the association between time-dependent diabetes and change in cognitive function (log(3MSE errors)), and hazard ratios (HR) to describe the association between time-dependent diabetes and cognitive decline and risk of death from mixed linear effects models.

	Model 1				Model 2				Model 3			
	AIC: 20599.2				AIC: 19672.1				AIC: 19638.4			
Parameter	b	95% CI		*p*-value	b	95% CI		*p*-value	b	95% CI		*p*-value
Intercept	2.420	0.025	2.420	<.0001	2.406	0.027	2.406	<.0001	2.397	0.029	2.397	<0.001
Time (years)	-0.151	0.012	-0.151	<.0001	-0.148	0.012	-0.148	<.0001	-0.151	0.012	-0.151	<0.001
Time^2	0.018	0.002	0.018	<.0001	0.018	0.002	0.018	<.0001	0.018	0.002	0.018	<0.001
Diabetes (TD)	0.032	0.039	0.032	0.416	0.051	0.035	0.051	0.146	0.050	0.035	0.050	0.161
Diabetes*Time	0.042	0.021	0.042	0.049	0.042	0.021	0.042	0.046	0.038	0.021	0.038	0.074
Diabetes*Time^2	-0.005	0.003	-0.005	0.072	-0.005	0.003	-0.005	0.073	-0.004	0.003	-0.004	0.114
Age (baseline, years)	-	-	-	-	0.024	0.002	0.024	<.0001	0.024	0.002	0.024	<0.001
Female sex	-	-	-	-	0.021	0.027	0.021	0.433	0.029	0.027	0.029	0.282
Education (years)	-	-	-	-	-0.076	0.003	-0.076	<.0001	-0.076	0.003	-0.076	<0.001
Large waist (baseline)	-	-	-	-	-	-	-	-	-0.016	0.028	-0.016	0.572
Stroke (TD)	-	-	-	-	-	-	-	-	0.185	0.043	0.185	<0.001
Diastolic blood pressure (TD, 10 mmHg)	-	-	-	-	-	-	-	-	0.027	0.009	0.027	0.004

TD=time-dependent; SD=standard deviation. Age, education, and diastolic blood pressure are centered at mean baseline values.
Model 1: unadjusted; Model 2: adjusted for age, sex, and education; Model 3: Model 2 + large waist circumference, stroke, diastolic blood pressure.

Chapter 3: Type 2 diabetes and cognitive decline over 14 years in middle-aged African Americans and whites: The ARIC Study

Introduction

A growing body of evidence suggests diabetes is associated with a higher incidence of cognitive impairment and dementia in late life (1-5). With the high and growing prevalence of diabetes in the U.S. (6) and the increase in dementia due to the aging of the population (7), the effect of diabetes on risk of dementia is of great public health importance. The etiologic link between diabetes and dementia has not been determined, but pathways that could explain this link include the effects of hyperglycemia and hyperinsulinemia and insulin resistance on the cerebrovasculature and beta-amyloid deposition in the brain (8, 9). Importantly, prevention and management of diabetes may affect the rate of cognitive decline and occurrence of dementia in older populations.

Most prior studies on diabetes and cognitive decline and dementia have focused on older adults, and the association between diabetes and cognitive decline in mid-life has not been thoroughly examined. Examining the effect of diabetes on cognitive decline in midlife, prior to the onset of substantial cognitive decline, is important for understanding how diabetes affects cognition earlier in the lifespan and may have implications for potential strategies to preserve cognitive function and to prevent or delay onset of dementia in late-life. Most previous studies have limited analyses to baseline diabetes, but recent studies have suggested that longer duration of diabetes is associated with greater decline (10-12). It is particularly important to study the relation between diabetes and cognitive decline in populations with a high burden of diabetes, as variation in the distributions of risk factors may impact the association. Compared to non-Hispanic whites, African Americans have a higher prevalence of diabetes (6), younger age at diagnosis (13), poorer quality diabetes care (14), and a higher risk of some diabetes complications (14).

The objective of this study was to evaluate the effect of both prevalent and incident diabetes on cognitive decline across three cognitive domains over 14 years in a biracial cohort of middle-aged adults, and whether the effect of diabetes and cognitive decline differs among African Americans and whites.

Methods

Study sample

The ARIC Study is a community-based cohort study of 15,792 white and African American middle-aged adults from four U.S. communities (Washington County, MD, Forsyth County, NC, suburbs of Minneapolis, MN, and Jackson, MS) that began in 1987-1989 and is ongoing. The ARIC study was designed to examine the etiology and clinical outcomes of atherosclerosis and differences in cardiovascular risk factors, care, and disease by race, gender, location, and date. A detailed description of the study design has been published (15). Cognitive function was first assessed at ARIC Exam 2 (1990-1992). Thus, ARIC Exam 2 serves as the baseline examination for the present analysis. At the following ARIC exam (1993-1995), ARIC participants aged 55 and older in two communities, Forsyth County, NC and Jackson, MS, were screened for eligibility for cerebral magnetic resonance imaging (MRI) examination. The ARIC MRI Study was designed to examine risk factors for progression of brain abnormalities and how progression relates to cognitive decline and stroke (16). ARIC MRI Study participants underwent cognitive assessments on additional occasions compared to other ARIC Study participants. A total of 1,930 people underwent cerebral MRIs and had scans of sufficient quality for grading. Study participants who underwent cerebral MRI had cardiovascular risk factor profiles similar to those who declined to participate (17). Individuals who underwent cerebral MRI were excluded from this analysis if they were missing baseline information on diabetes, education, hypertension, or waist circumference (n=38), if they did not have cognitive assessment information from any year (n=3), or if

they were not African American or white (n=3). The resulting sample size for this analysis was n=1,886 individuals. The flow of study measurements is described in Figure 3.1.

Cognitive function

ARIC MRI Study participants underwent cognitive assessments at baseline (1990-1992) and in years 3 (1993-1995), 6 (1996-1998), and 14 (2006-2008). Cognitive function was measured with three widely-used cognitive tests: the Delayed Word Recall Test (DWRT) (18), the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (19), and the first-letter Word Fluency Test (WFT) (20) of the Multilingual Aphasia Examination (21). The cognitive assessment procedures have been described in detail (22). The DWRT measures verbal learning and memory. Participants are read a list of 10 common nouns and are asked to recall the nouns after a 5 minute interval, during which the DSST was administered. The DWRT was scored as number of words recalled correctly; scores range from 0-10. The DSST is a test of processing speed. It is a paper and pencil task requiring timed translation of numbers (1-9) to symbols using a key and is scored as the number of numbers translated correctly within 90 seconds. Baseline scores in this sample ranged from 0 to 85. The WFT is a test of verbal fluency. The test consisted of three trials. Participants were asked to generate as many words as possible beginning with the letters F, A, and S within 60 seconds per letter. The test was scored as the total number of words generated for all three letters. Baseline scores in this sample ranged from 0-84.

Diabetes

At cognitive assessments 1, 2 and 3, participants were classified as having diabetes if they met at least one of the following criteria: 1) fasting glucose level ≥126 mg/dL, 2) non-fasting glucose level ≥200 mg/dL, 3) self-reported history of diabetes, or 4) use of anti-diabetic medication in previous 2 weeks. Participants with diabetes at the baseline cognitive assessment were classified as having prevalent

diabetes. Participants who were free of baseline diabetes and identified as having diabetes at the second or third cognitive assessment were classified as having incident diabetes.

Covariates

Demographic characteristics, including age, race, sex, and years of education were collected by interview at the baseline ARIC examination. At the baseline cognitive assessment, waist circumference was measured and history of stroke or myocardial infarction was ascertained from interview. Seated blood pressure was measured and hypertension was defined as systolic blood pressure ≥90 mmHg, diastolic blood pressure ≥140 mmHg, or anti-hypertension medication use.

Cerebral MRI measures included presence/absence of infarcts ≥3 mm and visual ratings of white matter hyperintensities, ventricular volume, and sulcal width. Images were read by trained neuroradiologists and scored on a semiquantitiave scale (graded from 0-9) (16). Consistent with previous ARIC publications (16, 23), MRI parameters were dichotomized as moderate to high abnormality/no to mild grade abnormality. Moderate to high abnormality was defined by grade 4 or higher for ventricular size, grade 3 or higher for sulcal size, and grade 3 or higher for white matter hyperintensities.

Mortality ascertainment

Mortality was ascertained through surveillance that included contact with next of kin and surveying discharge lists from local hospitals, local death notices, state health records, and the National Death Index. Death certificates were requested for all deaths.

Statistical Methods

The goal of this analysis was to evaluate the effect of diabetes (prevalent, incident, or no diabetes) on cognitive decline over 14 years and to examine whether the association between diabetes and cognitive decline differs by race in a biracial cohort of middle-aged adults.

We fit linear mixed effects models with random intercepts to examine the association between diabetes status and cognitive decline with time, in years, from the baseline cognitive assessment as the timescale. Attempts to fit models with random slope terms resulted in estimates of zero for the random slope variance. We included two-way interaction terms between diabetes and time to examine differences in cognitive decline by diabetes status. We fit an unadjusted model and a model adjusted for potential confounders: baseline age (centered at 60 years), sex (reference group = male), education (reference group = < high school graduate), waist circumference (centered at 96 centimeters), and hypertension (reference group = no hypertension). We considered adjusting for stroke and myocardial infarction, but the number of participants with a history of stroke or myocardial infarction was low, and adjustment for these variables did not influence estimates, so we did not include these variables in final models.

To examine whether the association between diabetes and cognitive decline differs by race, we fit models stratified by race. To formally test whether the association between diabetes and cognitive decline differs by race, we also fit models including both African Americans and whites and included three two-way (diabetes*race, race*time, time*diabetes) and one three-way interaction terms between race, diabetes, and time.

Our previous work has suggested that the observed association between diabetes and dementia could be altered by death (24). To examine the potential role of mortality, we fit an exponential survival model to examine the association between diabetes and risk of death. As in the linear mixed effects model, we used time from the baseline cognitive assessment as the timescale. We present results from race-specific models, and we also fit a model with both race groups and included a two-way interaction term for race*diabetes to formally test whether the association between diabetes and mortality differs by race.

As a sensitivity analysis, we used a joint longitudinal-survival model to simultaneously model cognitive decline and risk of death. This modeling approach accommodates selective survival effects by adjusting for participants who die earlier in the study period. The joint longitudinal-survival model was composed of two sub-models that used a shared random intercept for baseline cognitive function: a sub-model for the repeated measures of cognitive function (linear mixed effects model) and a sub-model for time to death (exponential model). The joint longitudinal-survival model was fit in SAS using PROC NLMIXED in SAS, following approaches described by Guo and Carlin (25).

Study participants were not systematically screened for dementia, but because the cohort was middle-aged, it is unlikely very many participants had dementia at baseline. In order to examine the association between diabetes and cognitive decline among people without cognitive impairment, we conducted a sensitivity analysis where we excluded participants who scored in the lowest 3% on baseline cognitive tests.

Results

Of the 1,886 participants, 16.8% of participants had prevalent diabetes (23.8% African Americans, 9.9% whites), 7.0% developed incident diabetes (8.5% African Americans, 5.4% whites), and 76.3% did not have diabetes (67.7% African Americans, 84.7% whites). At baseline, participants ranged from age 48 to 70. On average, people with prevalent diabetes had less education, and participants with prevalent diabetes, followed by those with incident diabetes, had larger waists and higher prevalence of hypertension (Table 3.1). History of stroke and myocardial infarction tended to be more common among people with prevalent diabetes. Cerebral MRI findings did not differ by diabetes status among African-American participants. Among white participants, those with prevalent diabetes had higher white matter grades and more ventricular enlargement. Compared to white participants, African American participants were slightly younger, more likely to be female, had less formal education, larger waist

circumferences, and more than twice the prevalence of hypertension. The prevalence of stroke and myocardial infarction did not differ by race, but more African American participants than white participants had small cerebral infarcts identified by MRI.

Among participants with prevalent diabetes, African Americans were more likely to be using an anti-diabetic medication and had average fasting blood glucose levels compared to whites (Table 2). Among participants with incident diabetes, anti-diabetic medication use and fasting blood glucose levels did not differ by race. At visit of diabetes diagnosis, anti-diabetes medication use was more prevalent and fasting blood glucose levels were higher among participants prevalent diabetes compared to those with incident diabetes.

The association between diabetes and cognitive change differed by cognitive test and race. Table 3.3 displays estimated regression coefficients (b) to describe the association between prevalent and incident diabetes and change in cognitive function over time (in years) from mixed linear effects models stratified by race. Predicted cognitive trajectories from the adjusted models are illustrated in Figure 3.2. Overall, African American participants scored lower on the cognitive tests at baseline and experienced more decline on the cognitive tests throughout the study compared to white participants. Among African American participants, diabetes was not associated with change over time on the DWRT (measure of verbal learning and memory), but those with prevalent diabetes experienced greater decline on the DSST (measure of processing speed) and the WFT (measure of verbal fluency) compared to those without diabetes. Over 14 years, those with prevalent diabetes declined by 1.7 more points on the DSST (equivalent to 45% greater decrease in DSST score) and 1.7 more points on the WFT (equivalent to 54% greater decrease in WFT score) (based on estimates from Model 2). Those with incident diabetes did not differ on cognitive change on any of the three tests relative to those without diabetes. Among white participants, neither prevalent nor incident diabetes was associated with accelerated cognitive decline on any of the three tests.

We tested the hypothesis that race modified the association between diabetes and cognitive decline with three-way interaction terms for race*diabetes*time for each cognitive test in overall (non-stratified) models adjusted for Model 2 covariates. Although we observed an association between diabetes and cognitive decline among African Americans but not whites, the interactions between race, diabetes, and time did not approach statistical significance: DWRT: race*prevalent diabetes*time p=0.515, race*incident diabetes*time p=0.496; DSST: race* prevalent diabetes*time p=0.480, race*incident diabetes*time p=0.820; WFT: race* prevalent diabetes*time p=0.134, race*incident diabetes*time p=0.689.

Participants were followed for a mean of 13.2 years (SD=2.2 years). Throughout the study period, 285 (15.1%) participants died (16.3% of African Americans and 14.0% of whites) and an additional 25.6% (n=483) participants withdrew from the study or were lost to follow-up (21.0% of African Americans and 30.1% of whites). Prevalent, but not incident, diabetes was associated with higher mortality rates for both African Americans and whites (Table 3.4). In fully-adjusted models, the association between prevalent diabetes and death was similar among African American and white participants.

We carried out several sensitivity analyses. To account for the potential influence of death on the association between diabetes and cognitive decline, we fit joint longitudinal-survival models to account for higher mortality rates among people with diabetes. Results from the joint longitudinal-survival models (Appendix) were similar to those from separate longitudinal models (Table 3.2). We also conducted a sensitivity analysis excluding participants with possible cognitive impairment at baseline. After excluding participants who scored in the lowest 3% on baseline cognitive tests, the association between prevalent diabetes and decline on the DSST (regression coefficient for time*prevalent diabetes=-0.157; 95% CI: -0.274, -0.039; p=0.009) and WFT (regression coefficient for time*prevalent diabetes=-0.111; 95% CI: -0.222, -0.001; p=0.049) remained among African Americans.

Discussion

In this biracial cohort of middle-aged adults followed for 14 years, prevalent, but not incident, diabetes was associated with accelerated decline in processing speed and verbal fluency among African Americans. This suggests that longer duration and greater severity of diabetes is associated with greater cognitive decline in midlife in this group. Among white participants, we observed virtually no change in cognitive test scores over the study period, and we did not observe an association between diabetes and cognitive decline.

There are several factors that may have contributed to our finding that prevalent diabetes was associated with accelerated decline in processing speed and verbal fluency among African Americans and not whites. African Americans with prevalent diabetes had higher fasting blood glucose levels and were more likely to be using anti-diabetes medications compared to white participants with prevalent diabetes. We did not have information on disease duration for participants with prevalent diabetes in this study, but in national survey reports, African Americans tend to be diagnosed with diabetes at younger ages than whites (13), so among members of this cohort with prevalent diabetes, African American participants may have had longer disease duration than white participants. These differences in diabetes characteristics by race suggest that the influence of diabetes on cognition began earlier and had more severe effects at younger ages in African Americans compared to whites. Additionally, overall, African Americans had lower initial cognitive test scores and more rapid decline over time compared to whites, which may reflect differences in the rate of cognitive aging between these two groups. African Americans had less education, more abdominal obesity, and had more than twice the prevalence of hypertension compared to whites. Although we controlled for these factors in our models, unmeasured social factors and comorbidities may contribute to the observed differences between African Americans and whites.

Our finding that prevalent, but not incident, diabetes was associated with accelerated cognitive decline in African Americans is consistent with recent studies that measured both prevalent and incident diabetes have found longer duration of diabetes is associated with accelerated cognitive decline (10-12). The relation between diabetes and cognitive decline in midlife has been previously examined in whites in the Framingham Offspring Study (26) and in a Dutch cohort study (12). The former study reported no association between diabetes and cognitive decline and the later study reported greater decline in global cognitive function and memory, but not processing speed. Several previous studies of older adults that have focused on older white populations have also reported that diabetes is associated with accelerated decline in processing speed (10, 11, 27), although some studies have reported no association (28, 29). Diabetes has been linked to accelerated decline in verbal fluency in older white women (30). Findings from studies of older adults examining diabetes and change in verbal memory are mixed, with some studies reporting an association (11, 28) and others reporting no association (27). Differences in the observed association between diabetes and change in specific cognitive domains across studies may be due to differences in the characteristics of the study population, including differences in age, social factors, comorbidities, and duration and severity of diabetes, and the specific neuropsychological tests used.

Knopman et al. previously investigated the relation between diabetes and cognitive decline in the ARIC cohort, and also found that baseline diabetes was associated with accelerated decline on the DSST and WFT, but not the DWR, over 14 years (31). The present paper builds on this previous paper in multiple ways. The present analysis examined the association between diabetes and cognitive decline among African Americans and whites separately and examined incident diabetes, in addition to diabetes that was prevalent at baseline. The two papers also differ with respect to the handling of death and dropout. The present analysis includes all participants (n=1,886) who participated in the ARIC MRI Study. The previous analysis was restricted to individuals who remained in the study through the final cognitive

assessment in year 14 (n=1,130). Additionally, the present study includes a sensitivity analysis in which we adjusted for the influence of mortality attrition using joint longitudinal-survival models.

This study has several notable strengths. ARIC is a community-based cohort study of middle-aged adults. Participants were followed starting in midlife, before the onset of substantial age-related cognitive decline, and were followed for up to 14 years. The analytical cohort was composed of substantial numbers of both African Americans and whites. Thus, our findings are generalizable to African American and white community-dwelling adults in these locations in United States. Further, we examined the effects of incident, in addition to diabetes prevalent at baseline. Cognitive function was assessed on up to four occasions using a cognitive battery that assessed three different cognitive domains.

This study has some limitations. The analytical sample was composed of individuals who agreed to undergo a cerebral MRI. Although study participants who underwent cerebral MRI had cardiovascular risk factor profiles similar to those who declined to participate, it is possible that participants included in this analysis differed from those who did not. Additionally, participants had to agree to a second cerebral MRI to participate in the fourth cognitive assessment. In addition to mortality-related attrition, which we accounted for in a sensitivity analysis, there was 25.6% attrition from loss to follow up and drop out. We examined differences by race, but the Jackson cohort was composed of only African Americans and the Forsyth County cohort included more whites than African Americans (15), so some of the observed differences by race may be due to differences between the two communities. Lastly, although we used a cognitive test battery composed of widely used cognitive tests, there was only one test per domain and not all cognitive domains were assessed.

Among community-dwelling middle-aged adults, prevalent, but not incident, diabetes was associated with greater cognitive decline over 14 years among African Americans, who had higher fasting blood glucose levels, higher prevalence of anti-diabetic medication use, and worse cardiovascular

risk profiles than whites in this cohort. Our results suggest that earlier onset of diabetes and more disease severity is associated with accelerated cognitive decline in midlife. Future studies should examine diabetes management strategies to preserve cognitive function among middle-aged adults, particularly in populations with a high burden of diabetes.

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Table 3.1. Baseline characteristics of the sample by diabetes status and race (n=1886).

	African American			*p*	White			*p*	African American	White	*p*
	No diabetes	Prevalent diabetes	Incident diabetes		No diabetes	Prevalent diabetes	Incident diabetes				
n	628	221	79		811	95	52		928	958	
Age (years), mean (SD)	59.2 (4.5)	59.5 (4.7)	59.4 (4.4)	0.626	60.6 (4.4)	61.1 (4.3)	59.9 (4.0)	0.256	59.3 (4.5)	60.6 (4.4)	<0.001
Female sex, %	61.78	69.7	63.3	0.109	57.46	48.4	46.2	0.084	63.8	56.0	<0.001
Education, %											
<High school graduate	37.9	46.2	36.7	0.047	13.2	24.2	21.2	0.009	39.8	14.7	<0.001
High school graduate or vocational school	24.7	27.6	27.9		42.4	46.3	40.4		25.7	42.7	
College	37.4	26.2	35.4		44.4	29.5	38.5		34.6	42.6	
Waist circumference (cm), mean (SD)	96.6 (12.3)	106.5 (12.6)	106.2 (13.1)	<0.001	92.4 (12.1)	104.7 (14.2)	100.4 (11.0)	<0.001	125.3 (58.4)	107.7 (29.8)	<0.001
Fasting blood glucose (mg/dL), median (IQR)	102 (96-109)	155 (133-245)	113 (105-119)	<0.001	100 (94-107)	142 (130-179)	110.5 (103-118.5)	<0.001	107 (98-122)	101 (95-110)	<0.001
Hypertension, %	48.9	64.7	63.3	<0.001	22.0	41.1	40.4	<0.001	53.9	24.8	<0.001
Prevalent stroke, %	1.3	5.4	2.5	0.002	1.2	6.3	3.9	0.002	2.4	1.9	0.450
Myocardial infarction, %	3.3	5.4	3.8	0.385	2.7	8.4	3.9	0.013	3.9	3.3	0.530
MRI measures*											
Infarcts present, %	15.1	17.7	11.4	0.394	9.4	12.6	5.8	0.379	15.4	9.5	<0.001
Ventricular enlargement grade 4-9, %	13.9	16.3	16.5	0.607	16.8	26.3	1.9	0.001	14.7	16.9	0.180
Sulcal grade 3-7, %	27.4	28.5	29.1	0.916	26.4	35.8	17.3	0.041	27.8	26.8	0.635
White matter grade 3-8, %	12.3	15.8	19.0	0.148	10.6	13.7	7.7	0.502	13.7	10.8	0.052

*Baseline MRI measurements taken at second cognitive assessment (year 3).

p-values are for chi-square tests for categorical variables, ANOVA for age and waist circumference, and Wilcoxon Test for fasting blood glucose.

Table 3.2. Diabetes characteristics at visit of diabetes diagnosis by prevalent vs. incident diabetes status.

	Prevalent diabetes		*p*	Incident diabetes		*p*	Prevalent diabetes	Incident diabetes	*p*
	African American	White		African American	White				
n	221	95		79	52		316	131	
Using anti-diabetic medication, %	59.9	36.3	<0.001	18.0	15.7	0.738	52.6	17.1	<0.001
Fasting blood glucose (mg/dL), median (IQR)	155 (133-245)	142 (130-179)	0.006	131.5 (126-151)	131.5 (126-140.5)	0.573	153 (131-224)	131.5 (126-148)	<0.001

p-values are for chi-square tests for anti-diabetic medication and Wilcoxon Test for fasting blood glucose.

Table 3.3. Linear mixed effects models for diabetes and annual cognitive change stratified by race (presented as b=regression coefficient).

	African American						White					
	Model 1			Model 2			Model 1			Model 2		
	b	95% CI		b	95% CI		b	95% CI		b	95% CI	
Delayed Word Recall Test												
Intercept	6.342***	6.224	6.459	6.038***	5.828	6.248	6.910***	6.819	7.002	6.548***	6.392	6.705
Time (years)	-0.060***	-0.071	-0.048	-0.062****	-0.073	-0.051	-0.040***	-0.049	-0.030	-0.041***	-0.051	-0.032
Prevalent diabetes	-0.548***	-0.779	-0.317	-0.480***	-0.703	-0.258	-0.496***	-0.782	-0.211	-0.293*	-0.573	-0.013
Incident diabetes	-0.083	-0.434	0.268	-0.039	-0.367	0.290	-0.145	-0.516	0.227	-0.038	-0.392	0.316
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	0.003	-0.022	0.028	0.004	-0.020	0.029	0.018	-0.017	0.053	0.019	-0.016	0.053
Time*Incident diabetes	-0.012	-0.047	0.022	-0.010	-0.044	0.024	0.006	-0.032	0.044	0.007	-0.030	0.045
Digit Symbol Substitution Test												
Intercept	31.572***	30.597	32.547	28.515***	26.962	30.068	47.383***	46.646	48.120	43.626***	42.423	44.829
Time (years)	-0.271***	-0.324	-0.219	-0.279***	-0.331	-0.227	-0.334***	-0.374	-0.295	-0.338***	-0.378	-0.298
Prevalent diabetes	-4.019***	-5.935	-2.103	-2.314**	-3.864	-0.764	-4.360***	-6.643	-2.077	-1.173	-3.188	0.842
Incident diabetes	-0.404	-3.312	2.504	0.267	-2.012	2.547	-1.233	-4.228	1.761	0.479	-2.075	3.032
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	-0.129*	-0.245	-0.014	-0.125*	-0.240	-0.010	-0.072	-0.221	0.077	-0.064	-0.213	0.085
Time*Incident diabetes	-0.010	-0.167	0.148	0.001	-0.156	0.158	-0.032	-0.191	0.126	-0.030	-0.188	0.128
Word Fluency Test												
Intercept	29.803***	28.783	30.822	28.307***	26.586	30.028	34.765***	34.007	35.523	31.907***	30.574	33.239
Time (years)	-0.227***	-0.276	-0.178	-0.232***	-0.281	-0.183	-0.021	-0.067	0.025	-0.025	-0.071	0.021
Prevalent diabetes	-3.496***	-5.496	-1.496	-1.794*	-3.492	-0.096	-3.904**	-6.250	-1.558	-1.194	-3.431	1.042
Incident diabetes	-3.412*	-6.454	-0.369	-3.172*	-5.674	-0.670	-1.837	-4.915	1.241	-0.253	-3.091	2.585
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	-0.127*	-0.235	-0.019	-0.125*	-0.232	-0.017	0.025	-0.145	0.195	0.029	-0.141	0.198
Time*Incident diabetes	0.104	-0.041	0.249	0.106	-0.039	0.250	0.054	-0.129	0.238	0.056	-0.127	0.239

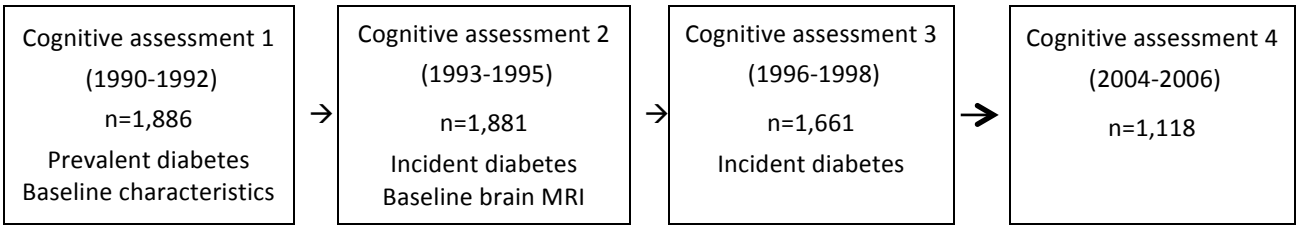
Model 1: unadjusted; Model 2: Adjusted for age (centered at 60 years), sex (reference = male), education (reference = intermediate education (high school graduate or vocational school)), waist circumference (centered at 96 cm), and hypertension (reference = no hypertension). *p < 0.05; **p < 0.01; ***p<0.001.

Table 3.4. Hazard ratios (HRs) relating diabetes and risk of death from exponential survival models stratified by race.

	African American						White					
	Model 1			Model 2			Model 1			Model 2		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Prevalent diabetes	1.88	1.34	2.64	1.78	1.24	2.55	2.81	1.87	4.25	1.86	1.20	2.88
Incident diabetes	1.11	0.61	2.03	1.08	0.58	2.00	1.72	0.90	1.30	1.37	0.70	2.66
No diabetes	ref			ref			ref			ref		

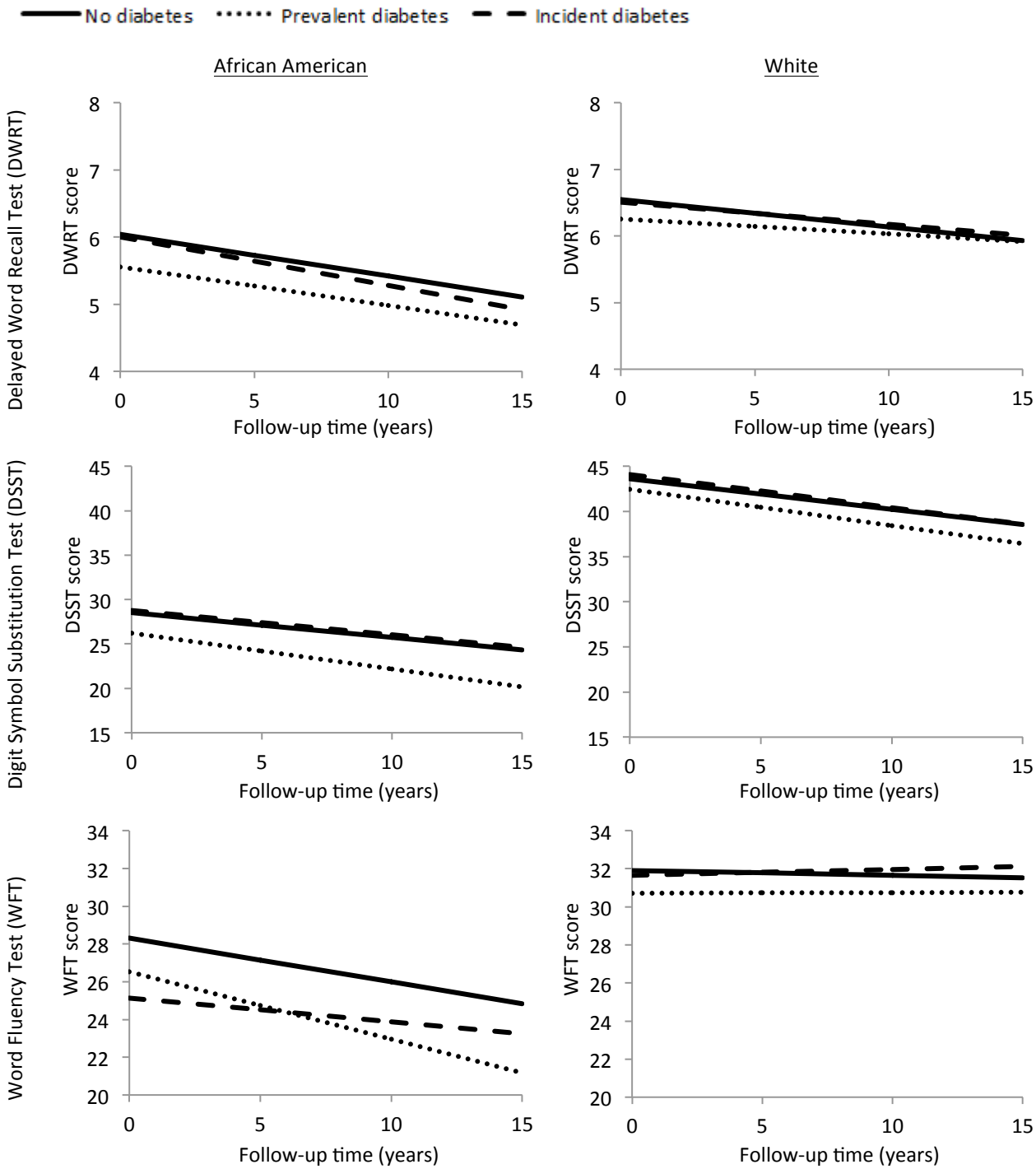
Model 1: unadjusted; Model 2: Adjusted for age, sex, education, waist circumference, and hypertension.

Figure 3.1. Flow chart of study measurements.



MRI = magnetic resonance imaging

Figure 3.2. Predicted cognitive trajectories by diabetes status from mixed linear effects models stratified by race and adjusted for age, sex, education, waist circumference, and hypertension. Shown for a 60-year-old male with intermediate education (high school graduate or vocational school), waist circumference of 96 inches, and without hypertension.



Supplementary Appendix

Table 3.5S. Results from the joint longitudinal-survival model results stratified by race (presented as b=regression coefficient).

	African American						White					
	Model 1			Model 2			Model 1			Model 2		
Delayed Word Recall Test												
Longitudinal sub-model	b	95% CI		b	95% CI		b	95% CI		b	95% CI	
Intercept	6.343***	6.226	6.461	6.037***	5.826	6.247	6.912***	6.820	7.004	6.549***	6.393	6.705
Time (years)	-0.061***	-0.073	-0.050	-0.063***	-0.074	-0.051	-0.041***	-0.050	-0.031	-0.042***	-0.051	-0.032
Prevalent diabetes	-0.547***	-0.778	-0.315	-0.479***	-0.702	-0.256	-0.495***	-0.781	-0.209	-0.290*	-0.571	-0.010
Incident diabetes	-0.079	-0.430	0.273	-0.037	-0.365	0.292	-0.139	-0.511	0.233	-0.036	-0.390	0.319
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	0.002	-0.023	0.026	0.003	-0.021	0.028	0.016	-0.019	0.051	0.018*	-0.017	0.053
Time*Incident diabetes	-0.013	-0.047	0.021	-0.010	-0.044	0.024	0.006	-0.032	0.043	0.007	-0.031	0.045
Survival sub-model	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Prevalent diabetes	1.89***	1.34	2.67	179*	1.25	2.58	2.89***	1.90	4.42	1.88***	1.21	2.93
Incident diabetes	1.12	0.61	2.08	1.09	0.759	2.04	1.75	0.90	3.42	1.37	0.70	2.68
No diabetes	ref			ref			ref			ref		
Baseline DWRT score	0.70***	0.59	0.82	0.80*	0.65	0.97	0.64***	0.53	0.78	0.80*	0.64	0.99
Digit Symbol Substitution Test												
Longitudinal sub-model	b	95% CI		b	95% CI		b	95% CI		b	95% CI	
Intercept	31.602***	30.627	32.578	28.575***	27.022	30.128	47.429***	46.691	48.166	43.623***	42.420	44.827
Time (years)	-0.277***	-0.329	-0.224	-0.283***	-0.335	-0.230	-0.339***	-0.379	-0.299	-0.341***	-0.381	-0.301
Prevalent diabetes	-4.053***	-5.971	-2.134	-2.303**	-3.855	-0.752	-4.695***	-6.981	-2.408	-1.255	-3.272	0.763
Incident diabetes	-0.581	-3.493	2.331	0.271	-2.010	2.552	-1.259	-4.259	1.740	0.431	-2.126	2.987
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	-0.134*	-0.249	-0.018	-0.128*	-0.243	-0.013	-0.070	-0.219	0.080	-0.064	-0.213	0.085
Time*Incident diabetes	-0.008	-0.165	0.150	0.001	-0.156	0.158	-0.032	-0.190	0.126	-0.029	-0.188	0.129
Survival sub-model	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Prevalent diabetes	2.11***	1.48	3.03	2.00***	1.38	2.91	3.00***	1.94	4.64	1.93**	1.23	3.01
Incident diabetes	1.19	0.62	2.26	1.15	0.60	2.21	1.65	0.83	3.30	1.44	0.73	2.82
No diabetes	ref			ref			ref			ref		
Baseline DSST score	0.96***	0.94	0.97	0.97**	0.94	0.99	0.94***	0.92	0.95	0.96***	0.94	0.98

Table 3.5S continued on next page

Table 3.5S continued from previous page

	African American						White					
	Model 1			Model 2			Model 1			Model 2		
Word Fluency Test												
Longitudinal sub-model	b	95% CI		b	95% CI		b	95% CI		b	95% CI	
Intercept	29.893***	28.873	30.912	28.345***	26.624	30.066	34.776***	34.018	35.535	31.936***	30.604	33.269
Time (years)	-0.231***	-0.280	-0.182	-0.233***	-0.283	-0.184	-0.025	-0.071	0.022	-0.027	-0.073	0.019
Prevalent diabetes	-3.738***	-5.740	-1.735	-1.750*	-3.449	-0.050	-3.931**	-6.280	-1.583	-1.270	-3.509	0.968
Incident diabetes	-3.351*	-6.396	-0.305	-3.156*	-5.660	-0.652	-1.902	-4.983	1.180	-0.316	-3.156	2.524
No diabetes	ref			ref			ref			ref		
Time*Prevalent diabetes	-0.127*	-0.235	-0.019	-0.127*	-0.235	-0.019	0.022	-0.148	0.192	0.028	-0.142	0.198
Time*Incident diabetes	0.103	-0.042	0.248	0.105	-0.040	0.250	0.054	-0.129	0.238	0.057	-0.126	0.240
Survival sub-model	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Prevalent diabetes	1.92***	1.35	2.71	1.81**	1.25	2.60	2.87***	1.89	4.36	1.90**	1.22	2.95
Incident diabetes	1.09	0.59	2.01	1.09	0.59	2.01	1.77	0.91	3.42	1.39	0.71	2.71
No diabetes	ref			ref			ref			ref		
Baseline WFT score	0.97***	0.96	0.99	0.98*	0.96	1.00	0.97***	0.95	0.98	0.98	0.96	1.00

Model 1: unadjusted, Model 2: Adjusted for age (centered at 60 years), sex (reference = male), education (reference = intermediate education (high school graduate or vocational school)), waist circumference (centered at 96 cm), and hypertension (reference = no hypertension). *p < 0.05; **p < 0.01; ***p<0.001.

From overall (non-stratified) models adjusted for Model 2 covariates the p-values for three-way interaction terms for race*diabetes*time for each cognitive test were as follows: DWRT race*prevalent diabetes*time p=0.516, race*incident diabetes*time p=0.496; DSST race*prevalent diabetes*time p=0.455, race*incident diabetes*time p=0.820; WFT race*prevalent diabetes*time p=0.688, race*incident diabetes*time p=0.130.

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