The effect of diabetes on the cognitive trajectory of older adults in societies of different aging contexts- A Study of Mexico and the U.S.

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ABSTRACT

Background: Mexico and the U.S. have very different aging and socioeconomic contexts. Mexico also has greater diabetes burden compared to the U.S, with similar diabetes prevalence but higher mortality. As diabetes is associated with poorer cognition, older Mexican adults might be at a greater risk for cognitive decline than their U.S. counterparts. However, no study has compared how diabetes impacts the cognitive trajectory of these countries, and which cognitive domains are important in this relationship.

Objective: The first objective is to examine the impact of diabetes on the total cognition score of older adults in Mexico and the U.S. The second objective is to examine this relationship by verbal memory and attention non-amnestic domains in both countries.

Methods: We used all waves of the Mexican Health and Aging Study for Mexico, and comparable waves of the Health and Retirement Study for the U.S. The outcomes were cognition measured as a standardized total cognition score, and as scores in standardized verbal memory and attention non-amnestic domains.

Results: Diabetes was associated with lower total cognition scores and attention non-amnestic scores at baseline and over time in both countries. However, the effect was mixed for the memory domain. In the MHAS, diabetes only predicted lower verbal memory scores over time, whereas in the HRS it only predicted lower scores at 65 years old. **Conclusion:** Diabetes impacted the long-term cognitive trajectory of older adults in both Mexico and the U.S. However, this trajectory was clearer for the attention non-amnestic domain in both countries.

INTRODUCTION

The risk of cognitive decline increases with age.[1] As the world population above 60 years old is expected to almost double from 12.3% in 2015 to 21.5% by 2050, cognitive health becomes a public health challenge.[1,2] By 2050, the number of people with dementia is also expected to double from 46.8 million to 131.5 million people.[1]

Changes in cognitive functioning are impacted by the socioeconomic and health context in which people age. Older adults with poor early-life SES are at a greater risk for poor cognition in later life.[3-5] In order to understand differences in cognitive health, there is a need to understand not only biological differences, but also how the culture, practices, structural factors and other facets of the aging context interact with the brain.[6] Specifically, it is important to consider the different life experiences individuals face over the lifespan, and how the brain adapts to different social contexts.[6] Yet, few studies have compared how cognition is determined by the aging context.

Mexico and the U.S. are good examples of different aging contexts because, while they are geographically close, they are at different stages of the demographic and epidemiologic transition, and are drastically different in socioeconomic terms.[7] In Mexico, population aging is occurring at a faster pace than in the U.S.,[7] in a context of low education[8] and increased mixed disease burden of both chronic and infectious[9] that older adults in the U.S did not experience as they aged.

Diabetes is a good example of the increased chronic disease burden in Mexico. Diabetes prevalence in Mexico is similar to that in the U.S. (nearly 25% in both countries in 2014)[10,11] but the disease-burden and mortality are higher in Mexico. In Mexico, diabetes is the second leading cause of death,[12] whereas in the U.S. it is the 7th

leading cause of death.[13] This difference in disease burden may be associated with late diagnosis and poor disease management in Mexico, as only 9.6% of adults with diabetes in Mexico reported having their HbA1C checked in the past year,[14] compared to 72.8% in the U.S.[15]

There is population-level evidence that diabetes impacts cognitive impairment, vascular dementia, Alzheimer's disease, and cognitive decline.[16-19] Further, there is mechanistic evidence that the micro and macro vascular damage caused by hyperglycemia is associated with brain infarctions and decrease blood flow to the brain;[20,21] and that insulin resistance is associated with the metabolism of beta-amyloid plaques present with Alzheimer's disease.[17]

The greater diabetes burden in Mexico may negatively impact the cognitive trajectory of older adults to a greater extent compared to the U.S. Poor diabetes management in the Mexican population also increases vascular risk, and the risk for diabetes-related comorbidities,[15] which may also add to the risk of cognitive decline in the Mexican population. Yet, the potentially different effects of diabetes on long-term cognition in these two countries is unknown.

Thus, the objective of this study is to examine the impact of diabetes on the cognitive trajectories of older adults in Mexico and the U.S, and determine if this relationship differs by domain (verbal memory and attentional non-amnestic domains). The first hypothesis is that diabetes will be associated with lower baseline cognition and greater decline over time in both countries. The second hypothesis is that diabetes will be associated with both verbal memory and attentional non-amnestic decline in both countries. The third hypothesis is that the strength of the association observed in

Mexico will be greater than the association observed in the U.S. due to a greater disease burden.

METHODS

Datasets

The Health and Retirement Study (HRS) was used to study the U.S. This is a nationally representative longitudinal cohort of older Americans above 50 years old. The HRS has a comprehensive questionnaire that covers topics of demographics, health conditions, cognition, disability, family structure and relationships, widowhood, socioeconomic factors, etc.[22] The American population has been followed biannually by the HRS since 1992. For this analysis, the 2000, 2002, 2012, and 2014 HRS waves were used in order to increase comparability with the Mexican data. The response rates for these waves were 85.4%, 86.6%, 89.6%, and 87.9%, respectively. The HRS adds a new cohort every six years. Thus, there were two new waves added between the waves selected: the early baby boomers in 2004, born 1942-1947; and the mid baby boomers in 2010, born 1954-1959.[22] The RAND HRS longitudinal file of 2014 was used in this study. This is a longitudinal cohort of the HRS merged and managed by RAND Corporation to facilitate data analysis and dataset comparability with other HRS sister studies. The RAND HRS fat files for each wave were utilized to select some variables that were not available in the longitudinal RAND HRS. [23]

The Mexican Health and Aging Study (MHAS) was used to study Mexico. This is a study highly comparable to the HRS in its study design, sampling procedure, and questionnaire, making cross-national comparisons easier. The MHAS is a nationally representative longitudinal cohort of community-dwelling older Mexican adults above 50

years old.[24] The cohort has been followed in 2001, 2003, 2012, and 2015. The response rate for each wave was: 91.8%, 93.3%, 88.1%, and 88.3%, respectively.[24,25] In 2012, a new refreshed sample of individuals born from 1952 to 1962 was added. [24] All waves were used for this analysis.

Sample Selection Criteria

The sample was restricted to older adults 50-100 years old in the MHAS and 49-100 years old in the HRS, with at least one direct interview, and at least one assessment of diabetes and cognition. Further, nursing home households in any of the selected waves were excluded in the HRS. The final sample size in the HRS was 17,634 in the year 2000, 16,594 in 2002, 19,052 in 2012 (from follow-up and those remaining from the new samples added in 2004 and 2010), and 17,346 in 2014. The final sample size in the MHAS was 13,008 in 2001, 12,035 in 2003, 13,355 in 2012 (from follow-up and the new sample from 2012), and 12,478 in 2015.

Dependent Variable

The outcome was cognition, measured by a total standardized cognition score and by domain (verbal memory and attentional non-amnestic) in each study.

In the HRS, cognition was measured with four tasks across selected waves independent of age: verbal learning (range 0-10), verbal recall (range 0-10), backward counting from 20 (range 0-2), and serial 7's subtractions (range 0-6). Other tasks are available in the HRS but these are only asked for individuals at or above 65 years old. Due to different ranges of scores across tasks, each task score was standardized.

The total standardized cognition score was calculated as the average of the four standardized task scores. Verbal learning and recall tasks measure the verbal memory

domain; and backward count and serial 7's measure attention/ working memory domain, which we refer to as attentional non-amnestic domain. The verbal memory domain score was calculated as the average of standardized verbal learning and verbal recall scores. The attentional non-amnestic domain score was calculated as the average of standardized backward count and serial 7's scores.

In the MHAS, cognition was measured with five tasks across all waves: verbal learning (range 0-8), verbal recall (range 0-8), visuospatial ability (range 0-2), visuospatial recall (range 0-2), and visual scanning (range 0-60). Due to different ranges of scores across tasks, each task score was standardized.

Preliminary data analysis indicated that the task of visuospatial recall should not be included in longitudinal data analysis due to change in scoring from 0-2 in the 2001/2003 waves to 0-6 in the 2012/2015 waves. Although the scores from the two last waves can be recoded as the scores from the first two waves, the recoding may introduce bias in a longitudinal data analysis as it shows that individuals with data in all waves are scoring higher in the last two waves compared to the first two waves, whereas the real explanation was a less conservative scoring. Due to possible bias, this task was excluded from the analysis. In order to measure the same domains in both datasets, the task of visuospatial ability was also excluded since it does not measure attention/working memory. However, a sensitivity analysis with the visuospatial domain was conducted for the longitudinal analysis in the MHAS.

The total standardized cognition score was calculated as the average of the three remaining standardized task scores (verbal learning, verbal recall, and visual scanning). The verbal memory domain score was calculated as the average of standardized verbal

learning and verbal recall scores. The attentional non-amnestic score was the score for the standardized visual scanning task, which also measures attention/working memory.

Independent Variable

Time varying self-reported diabetes status was the main independent variable in both studies. Respondents in both studies were asked: “Has a doctor or other medical professional ever/in the past two years told you that you have diabetes?” with answers being yes or no. However, in the MHAS, there were inconsistencies where individuals said they had diabetes in one wave and reported not having diabetes in a subsequent wave. In the present study, individuals that said they had diabetes at least two times in the MHAS were considered as having diabetes. As underdiagnoses of diabetes is high (nearly 18% of the sample in 2012),[26] we believe that those who said they had diabetes at least two times are more likely to indeed have diabetes.

Covariates

Time varying covariates similar to both datasets included: age; marital status (married, widowed, other); insurance status (uninsured, insured); comorbidity count categorized into 0, 1, 2+ (among stroke, heart disease, hypertension, and depressive symptoms); body mass index (obese, not obese); and visits to the doctor in the previous 2 years (yes, no). Death (yes; no) and loss to follow-up not due to death (yes; no) were also included as time varying covariates.

Sex; a continuous variable for years of education; and study cohort were also included as baseline covariates in both datasets.

In the MHAS, time varying locality size was included as an additional covariate (population <100,000 or ≥100,000). In the HRS, baseline race and ethnicity was included as an additional covariate (non-Hispanic black, non-Hispanic white, Hispanic).

Statistical Analysis

Baseline Analysis

Baseline data from MHAS 2001 and HRS 2000 were pooled, and weighted baseline characteristics were compared between datasets. This was the only pooled analysis conducted in this study. However, cognition was not directly compared between datasets as there are too many differences in the mode of interview and tasks asked between datasets to directly compare cognitive scores. Results were weighted according to each country's weight design.

Baseline data was also used to compare the total standardized cognition score across demographic and health characteristics within each country. T-tests were used to compare demographic and health variables across cognition scores in each dataset. Results were weighted according to each country's weight design.

Longitudinal Analysis

Longitudinal analysis was conducted with unweighted mixed-effect linear models in each country. This analysis accounts for within person variation over time and between person variations. Age, centered at 65 years old, was defined as the time variable, as seen in other longitudinal studies of aging.[27] All models included a random intercept and random slope for age. The covariance matrix was unstructured for all models.

First, similar models were fit for the MHAS and the HRS, including all common demographic and health covariates available in both studies. These models were conducted for the total standardized cognition score, and by domain. The model included all main effects, and the interaction between diabetes status and age to determine the annual change in cognitive decline by diabetes status.

Second, study-specific analyses were conducted to include the effect of locality size and diabetes management in the MHAS, and race and ethnicity in the HRS using the total standardized cognition score. The MHAS model included all main effects and the interaction between diabetes management and age. The HRS models included all main effects and the three way interaction between race and ethnicity, diabetes, and age. The sensitivity analysis in the MHAS with the visuospatial domain was an unweighted mixed-effect linear model, with only a random intercept. The model also included all main effects, and the interaction between diabetes status and age to determine the annual change in cognitive decline by diabetes status.

In order to better interpret the effect of diabetes on cognition in each country, predictive margins of cognition were estimated, holding the other covariates at their means. These estimates were then rescaled to express the effect of diabetes on cognition in terms of years of education. This does not change the results of the analysis, but allows us to reinterpret the effect of diabetes on cognition for each year increase in age. Specifically, each year increase in age is equated, by this rescaling, to the number of years of education associated with the same decrease in cognition.

This was done using the following STATA command:

margins diabetes, atmeans at(age=(65(10)95) expression (xb()/_b[edu])

where xb() is the linear prediction from the fitted model and the _b[edu] is the coefficient of education from the fitted model.

All analysis were conducted with STATA 14 (College Station, TX).

RESULTS

Baseline characteristics

Older adults in the HRS were more likely to be female and, on average, 3 years older than those in the MHAS (Table 1). Those in the MHAS had, on average, three times fewer years of education than those in the HRS (4.01 years vs. 12.43 years, $p<0.001$), and were almost five times more likely to be uninsured than those in the HRS (45.3% vs. 9.4%, $p<0.001$). There was no difference in diabetes prevalence between the two datasets, but those in the HRS were more likely to have two or more comorbidities (18.3% for MHAS vs. 22.1% for HRS, $p<0.001$) and be obese (22.2% vs. 25.5%, respectively, $p<0.001$). Older adults in the MHAS were 6 times more likely to say they had not visited a doctor in the past two years (36.8% vs. 6.0%, $p<0.001$) (Table 1). The other demographic and health characteristics were largely similar for both countries.

In the MHAS, those with diabetes had significantly lower total cognition score compared to those without diabetes (Table 2). The same was observed for the memory and attentional non-amnestic domains (not reported in tables). Females, the oldest old, the widowed, those with fewer years of education, the uninsured and those living in less urban areas had significantly lower total cognition scores compared to their counterparts. Those with diabetes that checked their blood sugar at least once per week

had higher total cognition scores than those without diabetes (0.01 vs. -0.12, p=0.003). The total cognition score significantly decreased as the number of comorbidities increased, and those with obesity had significantly higher cognition score than those not obese. There was no difference in total cognition score by frequency of doctor visit.

In the HRS, those with diabetes also had significantly lower total cognition score compared to those without diabetes (Table 2). The same was observed for the verbal memory and attentional non-amnestic domains (not reported in tables). Females, the oldest old, the widowed, those with fewer years of education, and the insured had significantly lower total cognition scores compared to their counterparts. Non-Hispanic blacks had the lowest total cognition scores, followed by Hispanics (-0.38 vs -0.24 respectively, and 0.13 for non-Hispanic whites, p<0.001). The total cognition score was significantly lower for those with higher number of comorbidities, but there was no difference in total cognition score by BMI. Those who did not visit the doctor in the previous two years had significantly lower cognition score than those who did.

Longitudinal Analysis

In the MHAS, those with diabetes had significantly lower total standardized cognition score at 65 years old compared to those without diabetes (β:-0.03, 95%CI: -0.05; -0.01). Diabetes was also associated with significantly greater decline over time for the total standardized cognition score (β:-0.003, 95%CI: -0.01; -0.002) (Table 3). The analysis by domain showed that, at 65 years old, diabetes was only associated with lower scores in the attentional non-amnestic domain (β:-0.07, 95%CI: -0.09; -0.05). However, over time, diabetes predicted lower scores in both the verbal memory and

attentional non-amnestic domains (β:-0.004, 95%CI: -0.01; -0.001; and β:-0.003, 95%CI: -0.005; -0.0004, respectively) (Table 3).

Being older and having more comorbidities was associated with lower cognition scores across the three outcomes (total cognition and both domains). On the other hand, having more years of education, being insured, and being obese was associated with higher cognition scores across the three outcomes. Women and those who visited the doctor in the previous two years were more likely to have higher cognition scores for total cognition and verbal memory domain, but there was no sex and health care use difference in the attentional non-amnestic domain. Widowhood only predicted lower cognition scores in the attentional non-amnestic domain (Table 3).

The impact of diabetes on the total standardized cognition score at 65 years old was equivalent to an average of 0.74 additional years of education. By 95 years old, this association was equivalent to an average of 12.4 fewer years of education (Figure 1). In the verbal memory domain, the same association was equivalent to an average of 3 to 14 fewer years of education between the ages of 75 to 95 (Figure 3). For the attentional non-amnestic domain, the association between diabetes and cognition was equivalent to 0.42 additional years of education at age 65, and 3 to 10 fewer years of education between ages 75-95 (Figure 5).

The MHAS specific analysis that included diabetes management and locality size showed that, at 65 years old, only those with diabetes that checked their blood sugar at least once per month had lower total cognition scores compared to those without diabetes (β: -0.04, 95%CI: -0.06; -0.02) (Appendix Table 1). However, this group had no significant cognitive decline over time, whereas those with diabetes that checked their

blood sugar at least once per week had the greatest decline in total cognition score over time (β: -0.01, 95%CI: -0.01; -0.004), followed by those with diabetes that checked their blood sugar once per year or never (β: -0.004, 95%CI: -0.01; -0.001) (Appendix Table 1). Further, those living in more urban areas were more likely to have higher total cognition scores compared to those in less urban areas (β: 0.10, 95%CI:0.08; 0.12) (not reported in tables). The sensitivity analysis with the visuospatial domain in the MHAS (standardized task of visuospatial ability as outcome) showed that, at 65, those with diabetes did not have lower visuospatial ability scores than those without diabetes. However, diabetes was associated with significantly greater decline over time for the visuospatial domain (β: -0.003, 95%CI:-0.01; -0.001) (not reported in tables).

In the HRS, those with diabetes had significantly lower total standardized cognition score at 65 years old compared to those without diabetes. Diabetes was also associated with greater decline over time (Table 4). The analysis by domain showed that, at 65 years old, diabetes was associated with lower scores in both the verbal memory and the attentional non-amnestic domains. However, over time, diabetes only predicted lower scores in the attentional non-amnestic domain (Table 4).

Being older and having more comorbidities were also associated with lower cognition scores across the three outcomes in the HRS. The same was observed for those widowed or divorced/single compared to those married/in a civil union. Having more years of education, being obese, and visiting the doctor in the last two years was associated with higher cognition scores across the three outcomes in this dataset. However, having insurance only predicted higher cognition score in the memory domain. Women had higher cognition score than men in the total standardized cognition

score and memory domain, whereas they had significantly lower scores than men in the attentional non-amnestic domain (Table 4).

The impact of diabetes on the total standardized cognition score at 65 years old was equivalent to, on average, 0.15 additional years of education. By 95 years old, this association was equivalent to an average of 7 fewer years of education (Figure 2). In the verbal memory domain, the same association at 65 years old was equivalent to an average of 0.33 additional years of education. For the attentional non-amnestic domain, the association between diabetes and cognition was equivalent to, on average, 0.25 additional years of education at age 65, and 1.27 to 3.3 fewer years of education between ages 75-95.

The HRS specific analysis that included race and ethnicity showed that, at 65 years old, non-Hispanic blacks and Hispanics had significantly lower total standardized cognition scores compared to non-Hispanic whites, with non-Hispanic blacks having the lowest cognition score (Figure 7). However, the interaction with diabetes at 65 years old showed that only Hispanics with diabetes had significantly lower cognition scores compared to Hispanics without diabetes. The interaction between race and age, and the three-way interaction between race and ethnicity, diabetes, and age were not significant (Figure 7).

DISCUSSION

In this cross-national study, we assessed the impact of diabetes on the cognitive trajectories of older adults in Mexico and the U.S. As hypothesized, diabetes predicted

lower total cognition scores at 65 and a significant decline in total cognition over time in both countries. However, contrary to the second hypothesis, we observed a domain-specific trajectory, where the trajectory of attentional non-amnestic domains in both countries was clearly affected by diabetes at baseline and overtime, and the trajectory in the verbal memory domain was mixed. In Mexico, the effect of diabetes on the memory domain was only observed over time, and in the U.S., this relationship was only significant at 65 years old.

It is established in the literature that diabetes is associated with cognitive decline.[16,18] We observed that diabetes was more consistently associated with attention/working memory tasks than for verbal memory. This finding is consistent with previous systematic reviews and meta-analysis that have observed diabetes is a greater risk factor for vascular dementia than for Alzheimer's disease (AD). A meta-analysis of longitudinal studies showed that the pooled relative risk associated with diabetes and vascular dementia was 2.48 (95%CI: 2.08-2.96), whereas the pooled relative risk for AD was 1.46 (95%CI: 1.20-1.77).[19] Further, out of 16 studies measuring AD in this meta-analysis, only six observed any association of diabetes with AD.[19] The primary cognitive symptoms of vascular dementia include impaired attention and executive functioning[28] whereas impaired learning and memory are the primary cognitive symptoms of AD.[29]

The stronger relationship of diabetes with vascular dementia can be explained by the important micro and macro vascular damage caused by diabetes that directly impact the brain, and increase the likelihood for other cerebrovascular diseases such as stroke.[17,19] A study of adults 85 years old and older showed that diabetes was only associated with lower cognitive score in tasks related to processing speed and

executive function, but not memory, reinforcing the observed stronger effect of diabetes on non-memory tasks.[30]

We also observed that the overall cognitive decline is steeper in Mexico independent of diabetes (equivalent to up to 12 fewer years of education in Mexico and up to 7 fewer years in the U.S. for total cognition, Figures 1 and 2). However, the difference in cognitive decline is similar between those with and without diabetes in both countries. At 65 years old, the difference in cognition score between those with diabetes and those without diabetes was equivalent to 0.39 fewer years of education in Mexico. In the U.S., this difference at 65 years old was equivalent of 0.62 fewer years of education. Over time the strength of the association in Mexico is equivalent to 0.87 to 1.84 fewer years of education for those with diabetes compared to those without diabetes; and 0.85 to 1.31 fewer years of education for those in the U.S.

The overall steeper decline in cognition in Mexico across domains may be associated with poor socioeconomic conditions through the life course, especially education and access to health care services. As seen in the baseline cross-national comparison, older adults in Mexico had the same disease prevalence of diabetes as those in the U.S. but presented very different socioeconomic contexts, with three times lower education and six times more uninsured than those in the U.S. Several studies have indicated that early-life conditions impact late-life cognition, and this relationship is especially mediated by adult socioeconomic characteristics (e.g. education) in adult life.[3,4,31] Further, a cumulative high SES was associated with a higher cognitive function over time,[31] which can explain the overall better cognition scores among older U.S. adults.

We observed similar sex differences in both countries. In the descriptive results, women were more likely to have higher mean total cognition scores than men in both countries. The same was observed in the longitudinal analysis for total cognition and the memory domain. However, there was no sex difference in the attentional non-amnestic domain in Mexico, and in the U.S., women had lower attentional non-amnestic domain scores than men.

The difference in domains between men and women has been observed in the literature with the MHAS, where women have higher cognition scores in the tasks of verbal learning and recall (used to calculate the verbal memory domain), whereas the difference is the opposite in the visual scanning task (the attentional non-amnestic domain in this study).[32,33] However, other MHAS studies using several tasks showed that women are more likely to have dementia.[34,35] In the HRS, there was no difference in dementia status by sex, [36,37] but women were less likely to have overall cognitive impairment.[38]

One of the limitations of this analysis is our inability to directly compare cognitive functioning between the two countries. This was not possible due to conceptual differences in the mode of interview, number of times a question was repeated and an overall different number and type of questions between datasets. Nevertheless, this study was the first to identify if the relationship between diabetes and cognition was present at 65 years old and over time in two countries of different aging contexts, and determine the magnitude of the association in both countries. Another limitation, especially in the MHAS, is the self-reported diagnosis of diabetes, which cannot be confirmed and can introduce bias due to inconsistencies across waves. However, we

minimized this bias by defining that those who reported diabetes at least two times were more likely to actually be diagnosed with diabetes. Further, the exclusion of respondents with all proxy interviews and institutionalized respondents may also be a limitation.

In conclusion, this study demonstrated that diabetes impacted the long-term cognitive trajectory of older adults in both Mexico and the U.S. However, the impact of diabetes was clearer for the trajectory of the non-memory domain in both countries. Although the overall decline in cognition was steeper in Mexico, the difference in cognitive decline between those with- and without- diabetes was similar in both countries.

The regularity of certain findings help us come closer to speculate that those patterns may be universal- regardless of the socioeconomic and life-course differences experiences by the population of older adults. We caution, however, that more research with cross-national comparisons is needed to continue to advance our knowledge of aging patterns in the world.

Table 1. Comparison of baseline demographic and health characteristics, weighted statistics, MHAS 2001 and HRS 2000

	MHAS 2001 (N=13,152)	**HRS 2000 (N=17,634)**	**p-value**[a]
Sex, (%)			
Male	47.0	43.7	0.001
Female	53.0	56.3	
Age, mean (SD)[a]	62.39 (14.5)	65.89 (8.3)	<0.001
Marital Status (%)			
Married/Partner	67.2	64.5	0.01
Widowed	18.8	19.4	
Other	14.0	16.1	
Years of education, mean (SD)	4.01 (6.5)	12.43 (2.6)	<0.001
Insurance Status			
Uninsured	45.3	9.4	<0.001
Insured	54.7	90.6	
Place of Residence			
Less Urban	53.5	NA	-
More Urban	46.5		
Race and Ethnicity			
Non-Hispanic white	NA	84.4	-
Non-Hispanic black		9.2	
Hispanic		6.4	
Diabetes, (%)			
No	86.6	86.8	0.7
Yes	13.4	13.2	
Frequency of Blood Sugar Check			
No DM	86.8	NA	-
DM, Checks per week	1.0		
DM, checks per month	7.9		
DM, checks per year/never	4.4		
Comorbidities			
0	44.1	40.2	<0.001
1	37.6	37.8	
2+	18.3	22.1	
BMI			
Not Obese	77.8	74.5	0.001
Obese	22.2	25.5	
Visited the Doctor in the past 2 years			
No	36.8	6.0	<0.001
Yes	63.2	94.0	

[a] Difference between baseline waves of MHAS and HRS at alpha ≤0.05; [b] Age at baseline ≥50 years old in MHAS and ≥49 years old in HRS; [c]

Table 2. Mean Standardized Total Cognition scores, MHAS 2001 and HRS 2000

	MHAS 2001		HRS 2000	
Socio Demographic Characteristics	**Mean Standardized Total Cognition (SD)**	**p-value**	**Mean Standardized Total Cognition (SD)**	**p-value**
Sex				
Male	-0.18 (0.82)	0.01	0.02 (0.63)	<0.001
Female	-0.11 (0.79)		0.08 (0.71)	
Age in years				
50-59	0.11 (0.76)	<0.001	0.24 (0.50)	<0.001
60-79	-0.29 (0.77)		0.04 (0.71)	
80-100	-0.91 (0.65)		-0.43 (0.78)	
Marital Status				
Married/ Civil Union	-0.07 (0.79)	<0.001	0.12 (0.64)	<0.001
Widowed	-0.40 (0.80)		-0.20 (0.76)	
Other (Divorced or Single)	-0.12 (0.82)		0.08 (0.63)	
Education(years in school)				
0-5	-0.37 (0.71)	<0.001	-0.88 (0.94)	<0.001
6	0.05 (0.79)		-0.59 (0.90)	
7+	0.47 (0.76)		0.09 (0.64)	
Insurance Status				
Uninsured	-0.31 (0.72)	<0.001	0.12 (0.64)	0.002
Insured	-0.005 (0.85)		0.02 (0.68)	
Place of Residence				
Less Urban	-0.28 (0.68)	<0.001	NA	
More Urban	0.01 (0.91)			
Race and Ethnicity				
Non-Hispanic white	NA		0.13 (0.61)	<0.001
Non-Hispanic black			-0.38 (0.99)	
Hispanic			-0.24 (0.82)	
Health Characteristics				
Self-reported Diabetes				
No	-0.12 (0.81)		0.08 (0.66)	<0.001
Yes	-0.23 (0.78)	0.002	-0.13 (0.73)	
Frequency of Blood Sugar Check				
No DM	-0.12 (0.81)	0.003	NA	
DM, Checks per week	0.01 (0.76)			
DM, checks per month	-0.24 (0.81)			
DM, checks per year/never	-0.26 (0.72)			
Comorbidities				
0	-0.04 (0.81)	<0.001	0.19 (0.60)	<0.001
1	-0.19 (0.79)		0.05 (0.66)	
2+	-0.26 (0.82)		-0.22 (0.77)	
BMI				
Not Obese	-0.07 (0.80)	<0.001	0.05 (0.68)	0.8
Obese	0.11 (0.79)		0.05 (0.68)	
Visited the Doctor in the previous 2 years				
No	-0.16 (0.81)	0.4	-0.02 (0.69)	0.002
Yes	-0.13 (0.81)		0.06 (0.67)	

Table 3. Linear mixed-effect models for standardized cognitive scores, total and by domain, Mexican Health and Aging Study

	Total Cognition β (95%CI)	**Verbal Memory Domain β (95%CI)**	**Attentional Non-Amnestic Domain β (95%CI)**
Intercept	**-0.60 (-0.64; -0.55)**	**-0.60 (-0.65; -0.55)**	**-0.56 (-0.62; -0.50)**
Diabetes			
No	Ref.	Ref.	Ref.
Yes	**-0.03 (-0.05; -0.01)**	-0.01 (-0.03; 0.02)	**-0.07 (-0.09; -0.05)**
Sex			
Male	Ref.	Ref.	Ref.
Female	**0.16 (0.14; 0.17)**	**0.24 (0.22; 0.26)**	-0.02 (-0.04; 0.001)
Age, years	**-0.03 (-0.03; -0.03)**	**-0.03 (-0.03; -0.02)**	**-0.03 (-0.03; -0.03)**
Marital Status			
Married/ Civil Union	Ref.	Ref.	Ref.
Widowed	-0.01 (-0.03; 0.01)	-0.004 (-0.03; 0.02)	**-0.03 (-0.05; -0.01)**
Other	-0.003 (-0.03; 0.02)	0.01 (-0.02; 0.04)	**-0.03 (-0.05; 0.00)**
Education, years	**0.07 (0.07; 0.07)**	**0.06 (0.06; 0.06)**	**0.10 (0.10; 0.10)**
Insurance Status			
Uninsured	Ref.	Ref.	Ref.
Insured	**0.06 (0.04; 0.07)**	**0.06 (0.04; 0.08)**	**0.06 (0.03; 0.08)**
Comorbidities			
0	Ref.	Ref.	Ref.
1	**-0.04 (-0.05; -0.02)**	**-0.04 (-0.06; -0.03)**	**-0.03 (-0.05; -0.02)**
2+	**-0.12 (-0.14; -0.10)**	**-0.12 (-0.14; -0.10)**	**-0.12 (-0.14; -0.10)**
BMI			
Not Obese	Ref.	Ref.	Ref.
Obese	**0.06 (0.05; 0.08)**	**0.06 (0.05; 0.08)**	**0.06 (0.04; 0.08)**
Visited the Doctor in the previous 2 years			
No	Ref.	Ref.	Ref.
Yes	**0.02 (0.01; 0.04)**	**0.04 (0.02; 0.06)**	-0.01 (-0.03; 0.01)
Diabetes*Age			
No Diabetes	Ref.	Ref.	Ref.
Yes Diabetes	**-0.003 (-0.01; -0.002)**	**-0.004 (-0.01; -0.001)**	**-0.003 (-0.005; -0.0004)**

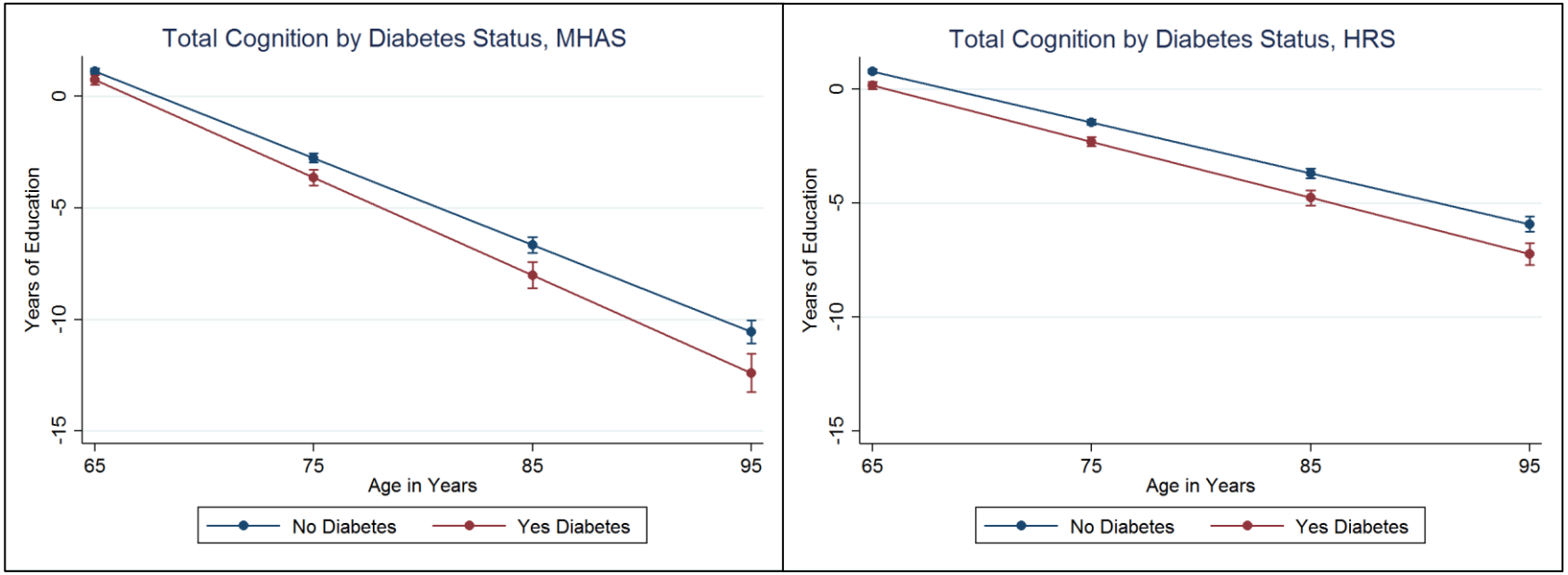
Also adjusted by: death, loss to follow-up, and study cohort.
Included random intercept and random slope for age. Age centered at 65 years old.

Table 4. Linear mixed-effect models for standardized cognitive scores, total and by domain, Health and Retirement Study

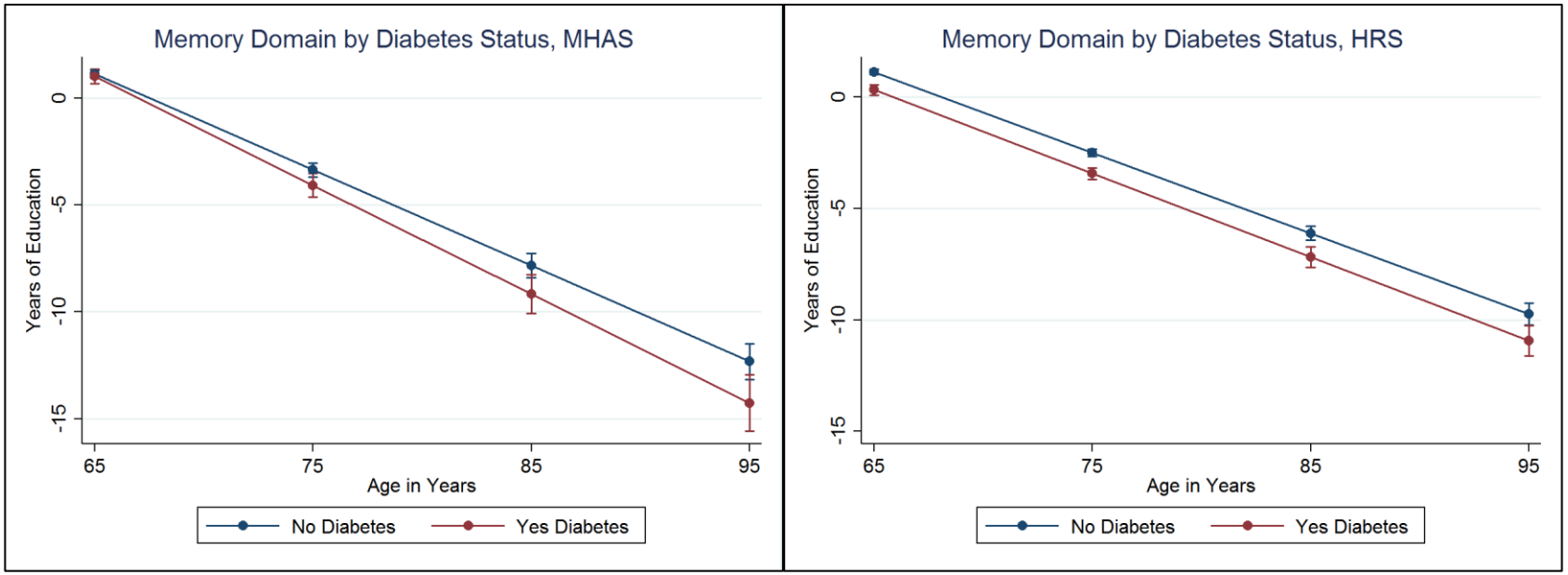
	Total Cognition β (95%CI)	**Verbal Memory Domain β (95%CI)**	**Attentional Non-Amnestic Domain β (95%CI)**
Intercept	**-1.12 (-1.17; -1.06)**	**-1.28 (-1.35; -1.21)**	**-0.99 (-1.05; -0.93)**
Diabetes			
No	Ref.	Ref.	Ref.
Yes	**-0.05 (-0.07; -0.04)**	**-0.07 (-0.09; -0.05)**	**-0.04 (-0.06; -0.03)**
Sex			
Male	Ref.	Ref.	Ref.
Female	**0.07 (0.06;0.08)**	**0.27 (0.25; 0.29)**	**-0.13 (-0.14; -0.11)**
Age, years	**-0.02 (-0.02; -0.02)**	**-0.03 (-0.03; -0.03)**	**-0.01 (-0.01; -0.01)**
Marital Status			
Married/ Civil Union	Ref.	Ref.	Ref.
Widowed	**-0.07 (-0.08; -0.05)**	**-0.08 (-0.10; -0.06)**	**-0.06 (-0.08; -0.05)**
Other	**-0.09 (-0.11; -0.08)**	**-0.10 (-0.12; -0.08)**	**-0.09 (-0.11; -0.07)**
Education, years	**0.08 (0.08; 0.09)**	**0.08 (0.08; 0.09)**	**0.08 (0.08; 0.08)**
Insurance Status			
Uninsured	Ref.	Ref.	Ref.
Insured	0.02 (-0.003; 0.03)	**0.04 (0.01; 0.06)**	-0.001 (-0.02; 0.02)
Comorbidities			
0	Ref.	Ref.	Ref.
1	**-0.05 (-0.06; -0.04)**	**-0.05 (-0.07; -0.03)**	**-0.05 (-0.07; -0.04)**
2+	**-0.15 (-0.17; -0.14)**	**-0.17 (-0.19; -0.15)**	**-0.14 (-0.16; -0.12)**
BMI			
Not Obese	Ref.	Ref.	Ref.
Obese	**0.03 (0.01; 0.04)**	**0.03 (0.01; 0.05)**	**0.02 (0.01; 0.04)**
Visited the Doctor in the previous 2 years			
No	Ref.	Ref.	Ref.
Yes	**0.08 (0.06; 0.09)**	**0.09 (0.06;0.11)**	**0.07 (0.05; 0.09)**
Diabetes*Age			
No Diabetes	Ref.	Ref.	Ref.
Yes Diabetes	**-0.002 (-0.003; -0.001)**	-0.001 (-0.003; 0.001)	**-0.002 (-0.004; -0.0004)**

Also adjusted by: death, loss to follow-up, and study cohort.
Included random intercept and random slope for age. Age centered at 65 years old.

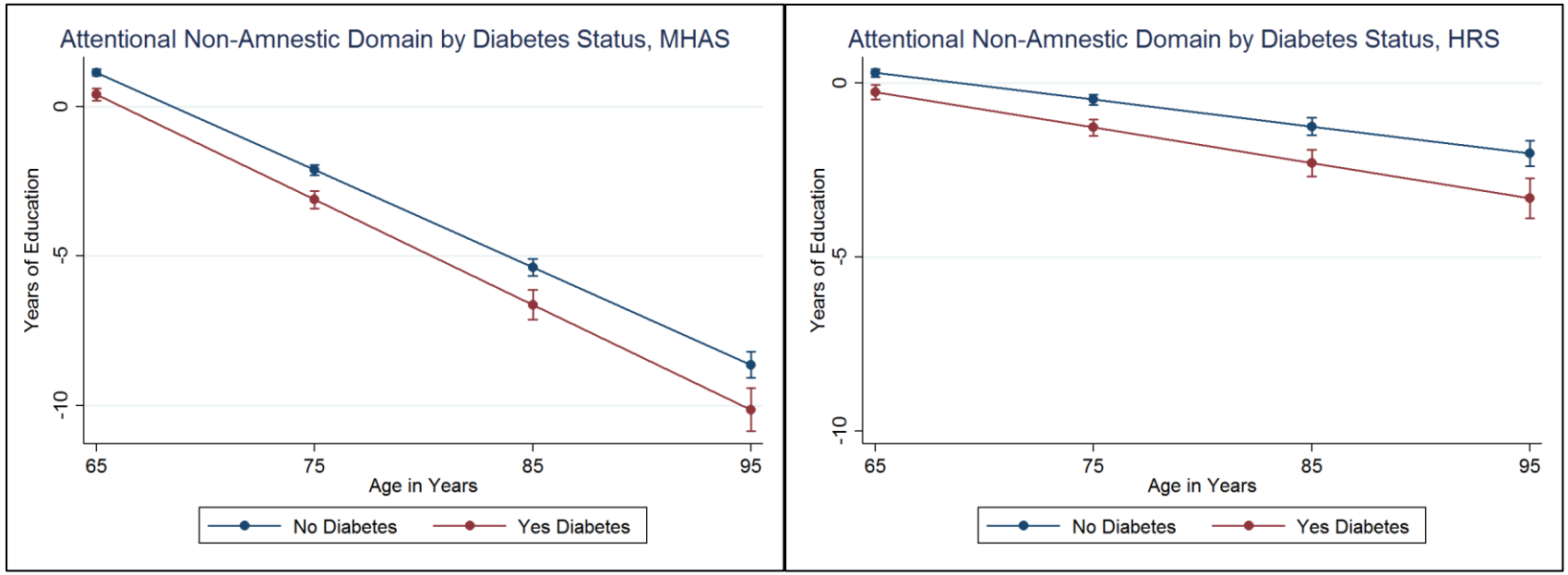
Figures 1 and 2. The effect of diabetes status on total cognition score in terms of years of education, MHAS and HRS



Figures 3 and 4. The effect of diabetes status on verbal memory domain in terms of years of education, MHAS and HRS



Figures 5 and 6: The effect of diabetes status on attention non-amnestic domain in terms of years of education, MHAS and HRS



All figures are predictive margins in terms of years of education, based results from Table 3 for MHAS and Table 4 for HRS. All results are adjusted for covariates included in those models.

Appendix Table 1. Linear mixed-effect models for total standardized cognitive scores, Mexican Health and Aging Study

Characteristics	Total Cognition β(95%CI)
Intercept	-0.64 (-0.68;-0.59)
At age 65	
No DM	**Ref.**
DM, Checks per week	-0.01 (-0.05;0.03)
DM, checks per month	**-0.04 (-0.06; -0.02)**
DM, checks per year/never	-0.02 (-0.05;0.01)
Over Time	
No DM	**Ref.**
DM, Checks per week	**-0.01 (-0.01; -0.004)**
DM, checks per month	-0.002 (-0.005; 0.000)
DM, checks per year/never	**-0.004 (-0.01; -0.001)**

Adjusted by: all common covariates and locality size.

Figure 8. Total standardized cognition score by Race and Ethnicity, and Diabetes Status, Health and Retirement Study

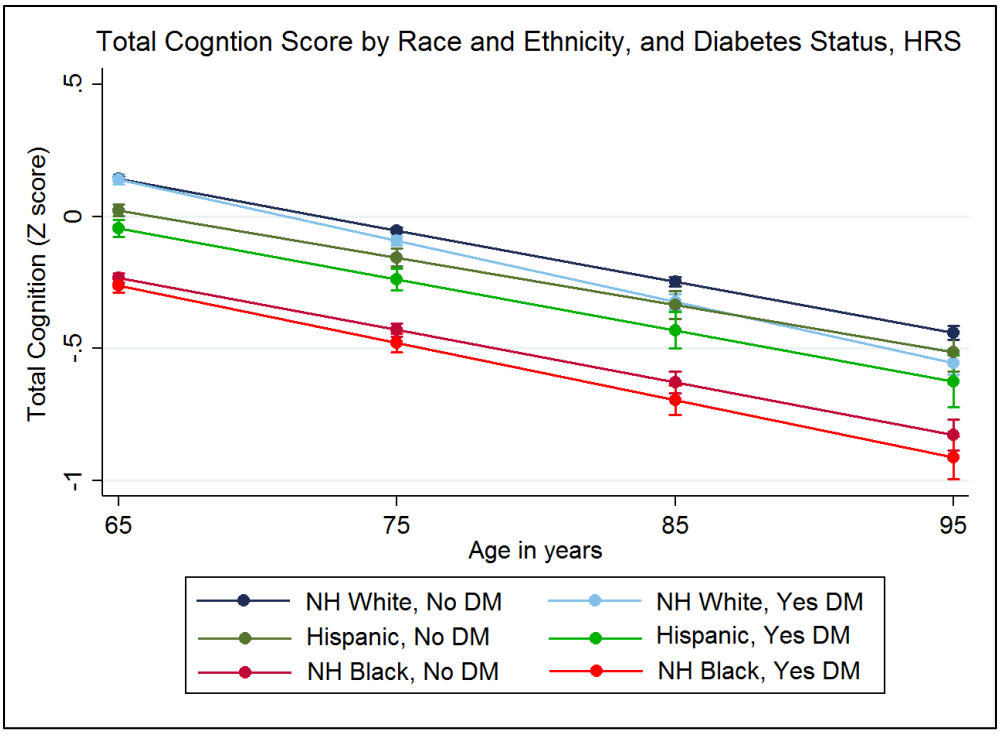


Figure based on predictive margins of the linear-mixed effect model, adjusted by all covariates.

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