Cumulative Effects of Metabolic and Vascular Risk Factors on Cognitive Decline among Older Mexican-Americans

Abstract

Objective: To examine the effects of metabolic and vascular conditions on cognitive decline among older Mexican Americans. **Methods:** The final sample included 2659 participants of the Hispanic EPESE. Linear mixed-effects regression was used to model cognitive decline across six examination waves (1993-2007) according to the number (zero, one, two, three-four) of metabolic and vascular risk factors (hypertension, diabetes, stroke, and heart attack). Effect sizes were based on the percent change in marginal variance for the linear mixed-effects model. **Results:** Participants with two or three-four risk factors had significantly greater cognitive decline compared to participants with zero risk factors. Stroke and diabetes increased the marginal variance by 2.1% and 1.2%, respectively. Hypertension and heart disease each increased the marginal variance by less than 1%. **Conclusion:** Mexican-American older adults with multiple metabolic and vascular risk factors exhibit greater cognitive decline than those with zero risk factors.

Background

Previous research indicates that diabetes, hypertension, stroke, and heart disease, are each associated with an increased risk for cognitive decline and dementia (Alonso et al., 2009; Biessels et al., 2006; Breteler, 2000; Elias et al., 2003; Gorelick et al., 2011; Yaffe et al., 2004). The vast majority of this research has focused on non-Hispanic populations and few studies have examined the effects of vascular and metabolic risk factors on cognitive functioning among Hispanic older adults. A study conducted by Nguyen et al. (2002) reported that Mexican-Americans with a history of diabetes or stroke were more likely to score 17 points or lower on the Mini-Mental Status Exam compared to participants without these conditions. These findings are consistent with other studies that have observed stroke and diabetes to be associated with an increased risk for major cognitive decline (Wu et al., 2003) and dementia (Haan et al., 2003) among Hispanic older adults.

Hypertension and heart disease have not been consistently observed to be independent risk factors for cognitive decline or dementia among Mexican-American older adults (Nguyen et al., 2002; Tang et al., 2001; Wu et al., 2003). However, hypertension and heart disease may negatively influence cognitive functioning when these conditions are comorbid with diabetes or stroke. This hypothesis is supported by evidence that metabolic syndrome, which is a cluster of metabolic and vascular conditions that increase the risk for cardiovascular disease (Grundy et al., 2004), is associated with a greater risk for dementia and cognitive decline among non-Hispanic white older adults (Raffaitin et al., 2009).

Hispanics are at an increased risk for metabolic and vascular conditions compared to non-Hispanic whites living in the United States (Fryar et al., 2010; Morgenstern et al., 2004; Narayan et al., 2003; Sundquist et al., 2001) and the prevalence of adults living with multiple metabolic and vascular conditions is highest among Hispanics (Mozumdar & Liguori, 2011). While there is evidence that vascular and metabolic conditions are independent risk factors for cognitive decline, the combined effects of these conditions on cognition among Hispanic older adults is less certain. Furthermore, it is not clear which metabolic or vascular risk factor has the greatest impact on cognitive decline. This study aims to address these questions using data from the Hispanic Established Populations for the Epidemiologic

Study of the Elderly (H-EPESE) to examine the individual and combined effects of diabetes, hypertension, stroke, and heart disease on cognitive decline.

Methods

The Hispanic Established Populations for the Epidemiologic Study of the Elderly

The H-EPESE is an ongoing longitudinal cohort study of community-dwelling Mexican-Americans 65 years of age and over residing in Texas, New Mexico, Colorado, Arizona, and California (Markides et al., 1997). The present analysis uses cognitive, demographic, and health status data collected during 6 examination waves from 1993 to 2007. A total of 3050 participants were evaluated during the first examination wave. Of these 3050 participants, 2852 completed the Mini-Mental State Examination (MMSE) and 2734 received an in person interview. The MMSE is a commonly used screening tool for cognitive impairment that measures orientation, registration, attention, calculation, recall, and language (Folstein et al., 1975). The MMSE was included during each examination wave.

Participants who needed to have a proxy complete the baseline examination (n=316) or did not receive the MMSE during the baseline examination (n=198) were excluded from the final sample. Remaining participants who had missing data for educational attainment, nativity (being born in the U.S.), smoking, alcohol consumption, marital status, language, or depression (n=65) were excluded from the final sample (n=2659). Participants excluded from the final sample were older, had less educational attainment, less likely to consume alcohol or to be married, and more likely to be depressed, have heart disease or have experienced a stroke compared to participants included in the final sample. However, participants excluded from the final sample were less likely to have hypertension during the baseline examination wave.

Metabolic and vascular risk factors

Diabetes, hypertension, stroke, and heart disease were each assessed during the baseline examination. Participants were classified as having diabetes if they responded *yes* to the question, "Have you ever been told by a doctor that you have diabetes, sugar in your urine or high blood sugar?" or if they were taking insulin. Participants were classified as having hypertension if they met one or more of the

following criteria: (1) responding *yes* to the question, "Has a doctor ever told you that you have high blood pressure?" (2) were taking anti-hypertensive medications; or (3) had an average systolic blood pressure ≥140 mmHg or average diastolic blood pressure ≥90 mmHG during the baseline examination. Stroke and heart disease were each assessed by self-report only. Participants who responded *yes* to the question, "Has a doctor ever told you that you had a stroke, a blood clot in the brain, or brain hemorrhage?" or "Has a doctor ever told you that you had a heart myocardial infarction, or coronary thrombosis?" were classified as having a stroke and heart disease, respectively. Participants who responded "maybe", "suspect", or "don't know" for stroke or heart attack (n=70) were classified as not having these conditions.

Risk factor summary score

The risk factor summary score was obtained by summing the number of metabolic and vascular risk factors reported by each participant. Only 12 participants had diabetes, hypertension, stroke, and heart disease and were therefore combined with participants who had 3 risk factors (n=101). A total of 756 participants had zero risk factors, 1266 had one risk factor, 525 had two risk factors, and 113 had three-four risk factors.

Covariates

Measures for several covariates were collected during the baseline examination. Age, educational attainment (no education, < high school, ≥high school), and sex (male, female) were included as covariates in all analyses. Smoking status was defined as never (< 100 cigarettes lifetime), former (> 100 cigarettes lifetime but not currently smoking), and current (>100 cigarettes lifetime and currently smoking). Alcohol consumption was defined as abstainer (never consumed alcohol), former (no alcohol consumed in the past year), and current (consumed alcohol in the past year). Marital status was categorized as never married, not married (separated, divorced, or separated), and currently married. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1977). Participants who had a total score greater than or equal to 16 on the CES-D Scale

were classified as having depressive symptoms. Finally, the language in which the participant chose the baseline examination to be conducted (English or Spanish) was included as a covariate.

Statistical analysis

Comparisons for demographic characteristics according to the number of metabolic and vascular risk factors during the baseline examination were made using Analysis of Variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Cognitive decline over time was modeled using linear mixed-effects regression models (Fitzmaurice et al., 2011). Linear mixed-effects regression is an effective approach for modeling longitudinal data because it accounts for differences in the number of observations and timing in which participants were observed. Time was measured as the number of years following the baseline examination. Random effects for time and intercept were included in all models to allow for the trajectory and baseline values for cognition to vary for each participant. Two-way interaction terms between time and the number of metabolic and vascular risk factors were included to determine if cognitive decline varied according to the number of metabolic and vascular risk factors.

The effect size of each metabolic and vascular risk factor on cognitive decline was based on the percent change in marginal variance for each risk factor. The percent change in marginal variance was obtained by first determining the marginal variance of the linear mixed-effects model that included time, age, sex, and education. This model served as the reference model. Next, a risk factor (diabetes, hypertension, stroke, or heart disease) was added to the reference model and the marginal variance was then calculated. The change in marginal variance between the two models allowed for the amount of variance attributed to each risk factor to be obtained. The percentage change in marginal variance for each risk factor was calculated according to the general equation:

$$PCMV = [(MVAR_{riskfactor} - MVAR_{ref}) / MVAR_{ref}] \times 100$$

Where: PCMV is the percentage change in marginal variance; MVAR is the marginal variance of the model; the *riskfactor* subscript represents the marginal variance for the model that includes one of the four risk factors and the subscript *ref* represents the marginal variance estimate for the reference model.

Results

Sample characteristics

A summary of the descriptive characteristics according to number of metabolic and vascular risk factors is provided in **Table 1**. The final sample was comprised mostly of females (n=1546, 58.2%) and the majority of the participants had less than a high school education (n=1974, 74.2%). Hypertension was the most common risk factor (n=1671, 62.8%) and diabetes was the second most common (n=638, 24.0%) during the baseline examination. Considerably fewer participants had a self-reported history of heart disease (n=230, 8.6%) and stroke (n=128, 4.8%). Statistically significant differences for sex, smoking, alcohol consumption, and depressive symptoms according to the number of metabolic and vascular risk factors were detected. Specifically, women were more likely to have one (OR=1.4, 95% CI=1.1-1.6) or two (OR=1.3, 95% CI=1.1-1.7) risk factors compared to men. Surprisingly, smoking had a protective effect and current smokers were less likely to have one (OR=0.51, 95% CI=0.39-0.66) or two (OR=0.48, 95% CI=0.33-0.67) risk factors compared to never smokers. Current alcohol consumers were less likely to have one (OR=0.74, 95% CI=0.60-0.93) or two (OR=0.57, 95% CI=0.42-0.77) risk factors, but former alcohol consumers were more likely to have three-four (OR=1.7, 95% CI=1.1-2.6) risk factors compared to abstainers. Finally, participants who had depressive symptoms were more likely to have two (OR=1.6, 95% CI=1.3-2.1) or three-four (OR=2.1, 95% CI=1.4-3.2) risk factors compared to participants without depressive symptoms.

Effects of metabolic and vascular risk factors on cognition

No statistically significant differences in the estimated baseline MMSE scores according to the number of metabolic and vascular risk factors were detected. However, there were significant differences in baseline MMSE score according to age, being born in the U.S., alcohol consumption status, marital status, and depressive symptoms (**Table 2**).

The predicted trajectories of cognitive decline according to the number of metabolic and vascular risk factors are presented in **Figure 1.** The severity of cognitive decline increased with the number of metabolic and vascular risk factors and statistically significant differences in cognitive decline according

to the number of risk factors were detected (F-value=13.5, *P*-value<0.01). Participants with two ($\hat{\beta}$=-0.17, SE=0.05, *P*-value<0.01) and three-four ($\hat{\beta}$=-0.61, SE=0.11, *P*-value<0.01) risk factors had significantly greater cognitive decline compared to participants with zero risk factors. Participants with one risk factor did not have significantly greater cognitive decline compared to participants with zero risk factors (**Table 2**).

A commonly cited limitation of the MMSE is the occurrence of a floor effect (Tombaugh & McIntyre, 1992). A potential consequence of this floor effect is the rate of cognitive decline among participants with a poor performance on the MMSE during the baseline examination will be underestimated. Therefore, the initial analysis was repeated with participants who scored 21 points or lower on the baseline MMSE were excluded from the model. A total of 476 (17.9%) participants scored 21 points or lower on the MMSE during the baseline examination. These participants were significantly older (75.3 vs. 72.5, F-value=84.3, *P*<0.01), more likely to abstain from consuming alcohol (60.1% vs. 53.0%, χ^2=15.9, *P*<0.01), report depressive symptoms (27.1% vs. 22.0%, χ^2=5.8, *P*<0.02), chose to have the interview conducted in Spanish (84.0% vs. 77.0%, χ^2=11.5, *P*<0.01), and more likely to have reported having a stroke (7.4% vs. 4.3%, χ^2=8.2, *P*<0.01) compared to participants who scored 22 points or higher on the MMSE. The results from the linear mixed-effects model that excluded participants who scored < 21 points on the MMSE were not qualitatively different from the original model. There were no statistically significant differences in baseline MMSE score according to the number of metabolic and vascular risk factors (F-value=0.91, *P*=0.43), but differences in the rate of cognitive decline according to the number of risk factors were statistically significant (F-value=12.35, *P*<0.01). Consistent with what was previously observed, participants with two ($\hat{\beta}$=-0.25, SE=-3.99, *P*<0.01) or three-four ($\hat{\beta}$=-0.58, SE=-4.59, *P*<0.01) risk factors had greater cognitive decline compared to participants with zero risk factors. A statistically significant difference in the rate of cognitive decline between participants with zero risk factors and those with one risk factor was not detected ($\hat{\beta}$=-0.02, SE=0.05, *P*=0.68).

Individual effects of metabolic and vascular risk factors on cognition

A summary of the individual effects of the metabolic and vascular risk factors on cognitive decline while controlling for the effects of age, sex, educational attainment, smoking, alcohol consumption, marital status, language, and depressive symptoms is provided in **Table 3**. No statistically significant differences in baseline MMSE according to hypertension, diabetes, stroke, or heart disease were detected. However, participants with diabetes or stroke had significantly greater cognitive decline compared to participants without these conditions. Participants with hypertension did not exhibit greater cognitive decline compared to those without hypertension. Finally, the effect of heart disease on cognitive decline approached statistical significance.

The marginal variance for the model that included time, age, sex, and education (reference model) was 0.197. The addition of hypertension, diabetes, stroke, and heart disease all significantly improved the fit of the reference model based on the reduction in AIC, but none of the risk factors increased the marginal variance of the reference model by more than 3%. Stroke increased the marginal variance of the reference model by 2.1%, diabetes increased the marginal variance by 1.2%, and both hypertension and heart attack increased the marginal variance by less than 1%. A full model that included all four risk factors increased the marginal variance of the reference model by 3.4%. The majority of marginal variance of the full model was explained by educational attainment, which increased the marginal variance by 24.1%. The percentage increase in marginal variance attributed to age was 3.4% and sex increased the marginal variance of the model by less than 1%.

Summary

This study presents new evidence that metabolic and vascular risk factors are associated with cognitive decline among Mexican American older adults. Participants who had two or three-four risk factors exhibited greater cognitive decline compared to participants with zero risk factors. Stroke and diabetes had the greatest impact on cognitive decline among the four metabolic and vascular risk factors. Interventions designed to reduce the prevalence of diabetes and stroke may decrease the severity of cognitive decline among older Hispanics.

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Table 1: Descriptive characteristics of final sample according to the number of metabolic and vascular risk factors.

	Number of Metabolic/Vascular Risk Factors					
Characteristic	Zero (n=756)	One (n=1266)	Two (n=525)	Three-Four (n=113)	F-value / χ^2-value	*P*-value
Age, mean (SD)	73.1 (6.3)	72.9 (6.4)	72.7 (6.0)	73.8 (5.8)	1.1	0.35
Sex, n (%)						
Male	353 (46.8)	498 (39.3)	207 (39.4)	55 (48.7)	**14.0**	**< 0.01**
Female	402 (53.2)	768 (60.7)	318 (60.6)	58 (51.3)		
Education, n (%)					11.2	0.08
None	143 (18.9)	179 (14.1)	79 (15.0)	16 (14.2)		
< High school	535 (70.9)	962 (76.0)	396 (75.4)	81 (71.7)		
≥ High school	77 (10.2)	125 (9.9)	50 (9.5)	16 (14.2)		
Smoking, n (%)					**32.7**	**< 0.01**
Never	400 (53.0)	769 (60.7)	321 (61.1)	62 (54.9)		
Former	216 (28.6)	361 (28.5)	151 (28.8)	38 (33.6)		
Current	139 (18.4)	136 (10.7)	53 (10.1)	13 (11.5)		
U.S. born, n (%)					7.6	0.06

No	329 (43.6)	578 (45.7)	205 (39.0)	44 (38.9)		
Yes	426 (56.4)	688 (54.3)	320 (61.0)	69 (61.1)		
Alcohol consumption, n (%)					**31.3**	**< 0.01**
Abstainer	390 (51.7)	706 (55.8)	291 (55.4)	56 (49.6)		
Former	166 (22.0)	292 (23.1)	149 (28.4)	40 (35.4)		
Current	199 (26.4)	268 (21.2)	85 (16.2)	17 (15.0)		
Marital status, n (%)					1.9	0.93
Never married	35 (4.6)	67 (5.3)	21 (4.0)	5 (4.4)		
Not currently married	290 (38.4)	497 (39.3)	202 (38.5)	44 (38.9)		
Currently married	430 (57.0)	702 (55.5)	302 (57.5)	64 (56.6)		
Depression symptoms, n (%)					**21.7**	**< 0.01**
No	608 (80.5)	990 (78.2)	377 (71.8)	75 (66.4)		
Yes	147 (19.5)	276 (21.8)	148 (28.2)	38 (33.6)		
Baseline cognition, mean (SD)	25.6 (3.9)	25.2 (3.7)	25.2 (3.9)	24.9 (4.2)	2.2	0.09

Bold indicates statistical significance $P < 0.05$. ANOVA was used for continuous characteristics and chi-squares for categorical characteristics. Percentages based on column totals.

Table 2: Combined effects of metabolic and vascular risk factors on cognitive decline.

Variable	Point estimate	Standard error	t-value	*P*-value
Time	-0.57	0.03	**-17.19**	**< 0.01**
Risk factors				
Zero (ref)	~	~	~	~
One	-0.26	0.15	-1.68	0.09
Two	-0.07	0.19	-0.36	0.72
Three-four	0.04	0.35	0.12	0.91
Time x risk factors				
Zero (ref)	~	~	~	~
One	-0.004	0.04	-0.11	0.91
Two	-0.17	0.05	**-3.09**	**< 0.01**
Three-four	-0.61	0.11	**-5.5**	**< 0.01**
Age	-0.11	0.01	**-10.8**	**< 0.01**
Sex				
Male (ref)	~	~	~	~
Female	0.47	0.16	**2.99**	**< 0.01**

Born in the U.S.				
No (ref)	~	~	~	~
Yes	0.40	0.13	**3.01**	**< 0.01**
Smoking status				
Never (ref)	~	~	~	~
Former	-0.08	0.16	-0.47	0.64
Current	-0.22	0.21	-1.04	0.30
Alcohol consumption				
Abstainer (ref)	~	~	~	~
Former	0.35	0.18	**1.98**	**0.05**
Current	0.74	0.19	**3.82**	**< 0.01**
Education				
< High school (ref)	~	~	~	~
None	-2.67	0.18	**-14.98**	**< 0.01**
≥ High school	2.32	0.22	**10.72**	**< 0.01**
Marital status				
Currently married (ref)	~	~	~	~
Not currently married	-0.51	0.14	**-3.51**	**< 0.01**
Never married	-0.72	0.30	**-2.38**	**0.02**
Language				
English (ref)	~	~	~	~
Spanish	-0.12	0.17	-0.74	0.46
Depressive symptoms				
No (ref)	~	~	~	~
Yes	-0.83	0.15	**-5.35**	**< 0.01**

Bold indicates statistical significance $P < 0.05$.
All of the variables listed in the table were included in the linear mixed-effects model.

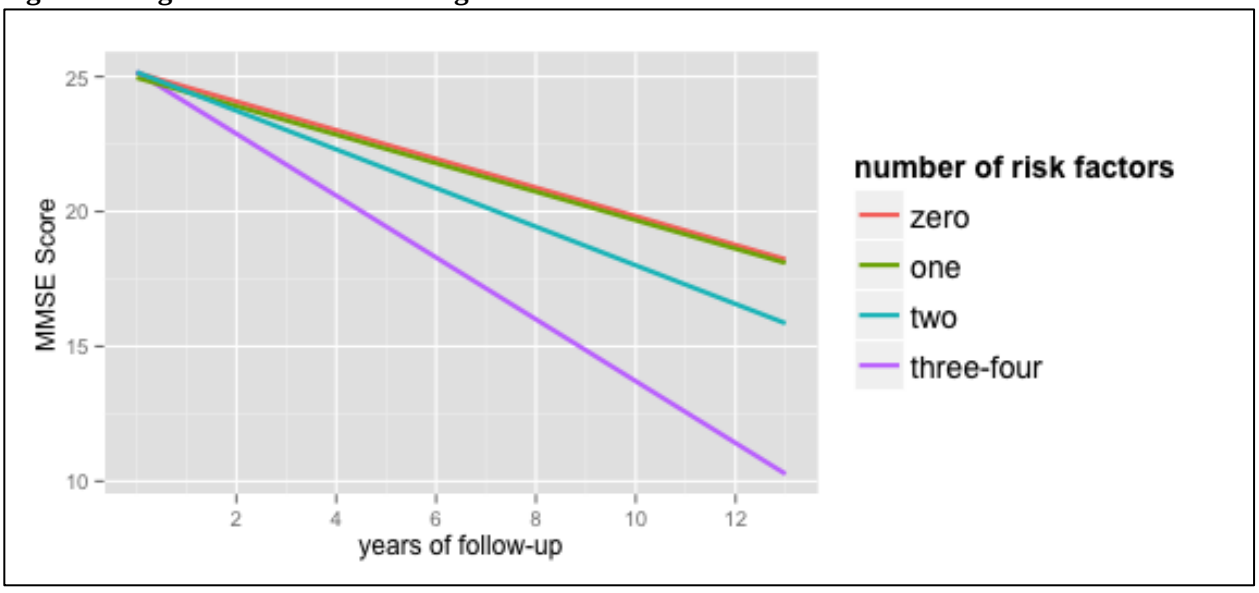
Table 3: Individual effects of hypertension, diabetes, stroke, and heart attack on cognitive decline

Variable	Point estimate	Standard error	t-value	*P*-value
Time	-0.54	0.89	**37.4**	**< 0.01**
Hypertension				
No (ref)	~	~	~	~
Yes	-0.21	0.14	-1.58	0.12
Diabetes				
No (ref)	~	~	~	~
Yes	0.20	0.16	1.29	0.20
Stroke				
No (ref)	~	~	~	~
Yes	-0.57	0.32	-1.79	0.07
Heart attack				
No (ref)	~	~	~	~
Yes	0.33	0.24	1.37	0.17
Time x hypertension				

No (ref)	~	~	~	~
Yes	-0.02	0.04	-0.63	0.53
Time x diabetes				
No (ref)	~	~	~	~
Yes	-0.17	0.05	**3.78**	< **0.01**
Time x stroke				
No (ref)	~	~	~	~
Yes	-0.35	0.10	**-3.65**	< **0.01**
Time x heart attack				
No (ref)	~	~	~	~
Yes	-0.13	0.07	-1.91	0.06

Bold indicates statistical significance $P < 0.05$.
Model controlled for the effects of age, sex, educational attainment, smoking, alcohol consumption, marital status, language, and depressive symptoms

Figure 1: Cognitive decline according to the number of metabolic and vascular risk factors



The predicted trajectories of MMSE over time according to the number of metabolic/vascular risk factors were obtained using the linear mixed-effects model that controlled for the effects of age, sex, educational attainment, smoking, alcohol consumption, nativity, language, marital status, and depressive symptoms.