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Research Article

Cardiovascular Risk Factors, Cognitive Dysfunction, and Mild Cognitive Impairment

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Keywords
Mexican American · Cardiovascular risk factors · Mild cognitive impairment

Abstract
Objectives: The present study sought to evaluate the contribution of cardiovascular risk factors to cognitive functioning in a sample of Mexican Americans diagnosed with mild cognitive impairment (MCI). ***Methods:*** Hypertension, diabetes, dyslipidemia, and obesity were diagnosed based on self-report and/or standardized procedures. Cognitive function was measured with MMSE, Logical Memory I and II, Trail A & B, FAS, animal naming, and digit span tests. Independent samples *t* tests and two-way ANOVAs were conducted for analyses, adjusting for relevant covariates. We studied 100 Mexican Americans (65 female) with MCI, ages 50–86, from a longitudinal study of cognitive aging conducted at the University of North Texas Health Science Center. ***Results:*** A difference between subjects with and without obesity and memory scores was shown by *t* tests. Two-way ANOVAs detected an association between the coexistence of hypertension and diabetes with language measures, diabetes and dyslipidemia with executive function, and diabetes and obesity with memory and language measures. ***Conclusions:*** This study provides additional evidence about the link between cardiovascular risk factors and cognitive dysfunction in MCI subjects, and also demonstrated that comorbid risk factors increased the degree of cognitive deficit in many areas, which may indicate a higher risk of developing dementia.

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Introduction

According to the Alzheimer's Association, by 2050, more than 13 million elders will be living with dementia in the USA [1]. Efforts to develop strategies to prevent or delay cognitive decline have become a priority. The first step should be to identify subjects at a greater risk of dementia. Mild cognitive impairment (MCI), defined as cognitive impairment without dementia, measured by neuropsychological tests, confirmed by health care providers/and or family members, with no interference in daily life activities [2], puts an individual at a greater risk of dementia [3]. Subjects with MCI have a higher incidence of cardiovascular risk factors (CVRFs) [4], and studies have shown a direct relationship between CVRFs and the risk of dementia [5, 6]. The impact that CVRFs such as diabetes mellitus, hypertension, dyslipidemia, and obesity have on cognition, has been elucidated [7], but the mechanisms for such impact are not clear for MCI subjects. One in 3 Americans have one or more types of CVRFs [5], and almost half of these individuals are 60 years or older. CVRFs should be major targets for therapeutic interventions to mitigate functional decline in cognitive ability.

Even though the impact of CVRFs on different target systems is not consistent, they do share pathological consequences such as atherosclerosis [7], inflammation [6], and altered metabolism [4]. The potential causes of cognitive changes associated to CVRFs are multifactorial, but cerebral macro- and microvascular disease, smaller brain volumes, the presence of inflammatory mediators, and amyloid deposition are consistently present [8–14]. Impairment of multiple cognitive systems are linked to CVRFs. Diabetes affects global cognition, memory, and visuospatial ability [15]. Most studies report an inverse relationship between hypertension status and cognitive performance on tests of attention, executive functions, visuospatial skills, psychomotor abilities, and perceptual skills [16]. Cholesterol level impacts a number of cognitive functions. A study based on the Framingham Heart Study cohort showed a significant association between total cholesterol and measures of verbal fluency, attention, and abstract reasoning [13]. Obesity indices were associated with poorer performance in global screening measures, memory, and verbal fluency tasks [17].

Hispanics are the second fastest growing ethnic group in the USA, and Hispanics of Mexican origin account for almost 65% of this population [18]. Most of the studies regarding the relationship between CVRFs and cognition were done in non-Hispanic whites. Mexican Americans have an increased burden of metabolic and vascular conditions [19]; therefore, it is important to add to the limited research on CVRFs and cognition in this population. Research has focused on Latino cognitive function related to CVRFs in cognitive normal subjects [20, 21], and there is a lack of research of the impact on CVRFs in subjects with MCI. Since well-established methods for the treatment and prevention of CVRFs are available, it is important to investigate the role of these factors in cognitive functioning of Mexican Americans.

The present study sought to evaluate the contribution of CVRFs to the degree of cognitive impairment in a sample of MCI Mexican American elders from a community-based study of cognitive aging. We hypothesized that CVRFs will have an impact on the degree on cognitive impairment in MCI-diagnosed Mexican Americans.

Materials and Methods

Study Design and Setting

Since 2012, an ongoing longitudinal study of cognitive aging has been conducted at the University of North Texas Health Science Center. This study uses a community based participatory research approach and recruitment methodology that has been previously described

[22]. Each participant undergoes an interview, medical history, neuropsychological testing, and fasting blood draw for clinical labs panel and inflammatory biomarkers. The study is conducted under the approval of the North Texas Regional IRB, 2012-183, and written informed consent was obtained from all participants included in this study.

Using the dataset from 2012 to 2015, we conducted a cross-sectional design investigation on data from 100 participants. Participants selected from the final analysis were Mexican American, over 50 years of age, and diagnosed with MCI during a consensus review according to published criteria [23].

Study Population

From May 2012 through June 2015, 771 participants were admitted to the study. Five hundred fifty-nine participants were Mexican American (participants who were born in Mexico or have Mexican ancestors), and 212 were non-Hispanic White. From the 559 Mexican American subjects, 415 were normal controls, 100 were diagnosed as MCI, 40 had Alzheimer's disease, and 4 subjects did not have enough data to make a cognitive diagnosis. The final sample for analysis consisted of 100 MCI Mexican Americans (65 females), with ages ranging from 50 to 86, and available neuropsychological tests scores.

Predicting Variables

Hypertension, diabetes mellitus, dyslipidemia, and obesity were used to predict neuropsychological test scores among Mexican American participants diagnosed with MCI. Hypertension was classified via self-reported medical history, use of blood pressure-lowering drugs, and/or average of 2 blood pressure measurements >140/90 mm Hg. Self-reported medical diagnosis, current use of insulin or oral hypoglycemic agents, and/or HbA1c >6.5% were used to diagnose diabetes. Participants with a medical diagnosis of high cholesterol and/or triglycerides, use of cholesterol-lowering drugs, and/or total cholesterol >200 mg/dL, and triglycerides >150 mg/dL were diagnosed as having dyslipidemia. Obesity was defined as having a body mass index of 30.0 or higher [24].

Cognitive Function

Global cognition was measured with the Mini Mental State Examination (MMSE), a widely used test in clinical and research settings [25]. To assess immediate and delayed memory, Logical Memory I and II from the Wechsler Memory Scale III (WMS III) were used [26]. The WMS III Digit Span was used as a measured of attention [27]. FAS and animal naming tests were used to evaluate language fluency [28]. Trails B test was used to assess executive function [29].

Covariates

Demographic information including age, gender, education level, and medical history were obtained during the interview.

Statistical Analysis

Demographic data were analyzed using *t* tests for continuous variables and χ^2 for categorical variables. An independent sample *t* test was used to determine whether there was a significant difference in the neuropsychological test means between participants with and without hypertension, diabetes, dyslipidemia, and obesity. Two-way ANOVAs were conducted to analyze if there was an additive interaction between two predicting variables and cognitive tests scores. We used cognitive test scale scores (Logical Memory I and II, Trails B, digit span, FAS, and animal naming tests), and raw total scores (MMSE test) stratified by education and age that were generated for Texas-based Mexican Americans [30]. Significant differences

Table 1. Demographics

	Mexican American Control (415)	Mexican American MCI (100)		95% CI	*p* value
Age, M (SD)	59.22 (6.97)	65.61 (8.45)	$t = 8.18$	5.01 to 8.18	<0.0001*
Education, M (SD)	8.35 (4.30)	6.37 (3.99)	$t = -4.27$	–2.92 to –1.08	<0.0001*
HTN, *n* (%)	279 (67.2)	84 (84)	$\chi^2 = 11.5$	7.74 to 24.53	0.0007*
DM, *n* (%)	171 (41.2)	42 (42)	$\chi^2 = 0.12$	–8.46 to 12.63	0.72
Dyslipidemia, *n* (%)	313 (75.4)	75 (75)	$\chi^2 = 0.00$	–9.86 to 8.62	0.98
Obesity, *n* (%)	229 (59.2)	53 (53)	$\chi^2 = 1.33$	–4.25 to 16.96	0.24

M, mean; SD, standard deviation; HTN, hypertension; DM, diabetes mellitus.

were indicated when the 2-sided *p* values were equal or less than 0.05. All models were adjusted for age, gender, and education level. The data were analyzed with SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographics

Table 1 presents the demographics of cognitive normal and MCI participants. Significant differences were found in mean age (59.22 for controls and 65.61 for MCI) and years of education (controls 8.35 vs. MCI 6.37). While no significant differences were found in the prevalence of diabetes, dyslipidemia, nor obesity, that was not the case for hypertension. Eighty-four percent of MCI participants had a hypertension diagnosis, compared with 67% of controls.

t Test Results of the Difference between Groups

Results of independent samples *t* test showed no significance difference between the cognitive test mean scores and the presence of hypertension, diabetes, and dyslipidemia (Table 2). There was a significant difference in immediate memory as assessed by Logical Memory I scores (M = 7.03, SD 3.32 vs. M = 8.80, SD 3.10; $t(98) = 2.60$, $p = 0.011$) in participants with and without obesity. Delayed memory as assessed by Logical Memory II scores also showed a significant difference between obese (M = 6.03, SD 3.33), and non-obese participants (M = 7.80, SD 3.27; $t(98) = 2.54$, $p = 0.013$).

Two-Way ANOVA Results of the Effect of Two Independent Variables on Cognitive Scores

A two-way ANOVA was conducted to examine the additive effect of the co-occurrence of two CVRFs on cognitive test scores (Table 3). In subjects with a diagnosis of hypertension and diabetes, there was a statistically significant difference on FAS ($F(1,94) = 5.14$, $p = 0.026$) and animal naming ($F(1,96) = 4.62$, $p = 0.034$). When diabetes and dyslipidemia diagnosis were present, only Trails B was significantly affected ($F(1,60) = 5.17$, $p = 0.026$). Logical Memory I and animal naming scores ($F(1,89) = 6.49$, $p = 0.013$ and $F(1,89) = 4.86$, $p = 0.030$, respectively) were significantly affected by the effects of diabetes and obesity together. The additive effect of dyslipidemia and obesity was only found for the digit span scale scores ($F(1,89) = 8.54$, $p = 0.004$). Finally, the co-occurrence of hypertension and dyslipidemia, and hypertension and obesity did not have a significant effect on cognitive scores.

Table 2. Independent *t* test between subjects with and without cardiovascular risk factors

	Hypertension			Diabetes			Dyslipidemia			Obesity		
	yes (n = 84)	no (n = 16)	t	yes (n = 42)	no (n = 58)	t	yes (n = 75)	no (n = 25)	t	yes (n = 53)	no (n = 40)	t
MMSE												
Mean	23.5	22.3	−1.25	24.09	22.82	−1.72	23.54	22.80	−0.88	23.60	23.62	0.00
SD	3.57	4.02		3.33	3.81		3.44	4.26		2.94	3.92	
Logical Memory I												
Mean	7.83	7.12	−0.80	8.07	7.50	−0.85	7.90	7.24	−0.87	7.03	8.80	2.60*
SD	3.35	3.19		3.03	3.51		3.32	3.29		3.32	3.10	
Logical Memory II												
Mean	6.78	6.50	−0.31	7.07	6.50	−0.83	6.96	6.08	−1.13	6.03	7.80	2.54*
SD	3.46	2.85		3.32	3.38		3.39	3.22		3.33	3.27	
FAS												
Mean	8.09	8.06	−0.05	8.29	7.94	−0.56	8.09	8.08	−0.02	7.88	8.61	1.15
SD	3.04	2.81		3.11	2.92		3.07	2.94		3.10	2.80	
Animal naming												
Mean	9.14	9.56	0.49	9.45	9.03	−0.66	9.28	9.00	−0.38	9.33	8.97	−0.55
SD	3.01	3.68		3.20	3.06		3.07	3.27		3.13	3.10	
Trails B												
Mean	4.74	5.33	−0.06	5.03	4.61	−0.47	4.96	4.18	−0.66	5.54	4.03	−1.67
SD	3.53	3.46		3.76	3.26		3.44	3.91		4.10	2.64	
Digit span												
Mean	7.73	7.68	−0.06	7.35	8.00	1.02	7.54	8.28	1.03	7.84	7.62	−0.34
SD	3.06	3.28		2.89	3.21		2.98	3.36		3.16	3.09	

* Significance $p \leq 0.05$. SD, standard deviation.

Discussion

The present study examined the role of hypertension, diabetes, dyslipidemia, and obesity on the severity of cognitive impairment among older Mexican Americans with an MCI diagnosis.

Obesity is associated with worse memory function [31]. Specifically, among MCI subjects, studies showed a difference in memory measures among MCI subjects with and without obesity [32], findings that are in agreement with the observations in our cohort. At the moment, it is not clear what drives the associations between weight and memory, and whether obesity affects cognition independently from other risk factors. Future studies should take into account a variety of covariates, like physical activity, energy intake, inflammation biomarkers, to try to understand the intersection between aging, obesity, and cognition.

Hypertension is a well-known risk factor for MCI [33], and research showed that adults with MCI and elevated blood pressure have a higher risk of developing dementia [34], suggesting that hypertension may impact the degree of cognitive impairment in MCI subjects. Our findings did not support this idea. We did not find a significant difference in cognitive measures among subjects with and without hypertension. The discrepancy may be explained by the difference in cohorts (e.g., community base versus clinical base) and different methodology used. Our analyses did not take in account the components, systolic and diastolic blood pressure, and treatment status. Our cohort is part of an ongoing longitudinal study. Future analyses are needed to determine the incidence rate of MCI -dementia conversion in subjects with and without hypertension.

Research has shown that diabetes is associated with an increased risk of cognitive impairment, MCI, and dementia, and progression from MCI to dementia is higher in subject with diabetes [35]. In our study we found a lack of association between having diabetes and

Table 3. Two way ANOVA of test scores by co-occurrence of cardiovascular risk factors

	Hypertension plus diabetes			Diabetes plus dyslipidemia			Diabetes plus obesity			Dyslipidemia plus obesity		
	yes (n = 37)	no (n = 37)	F	yes (n = 37)	no (n = 20)	F	yes (n = 24)	no (n = 24)	F	yes (n = 42)	no (n = 11)	F
MMSE												
Mean	24.70	23.54	8.71*	24.32	22.90	1.03	24.70	23.50	1.36	23.45	22.54	1.71
SD	2.74	3.47		3.04	4.16		3.61	3.23		3.95	3.69	
Logical Memory I												
Mean	8.40	7.81	2.77	8.00	6.90	0.68	8.16	9.33	6.49*	7.38	8.54	0.68
SD	2.97	3.21		3.01	3.25		3.04	3.21		3.45	3.61	
Logical Memory II												
Mean	7.21	6.72	0.57	7.05	5.80	0.42	6.95	8.16	3.50	6.50	7.72	1.76
SD	3.42	3.10		3.29	3.08		3.23	3.17		3.45	3.31	
FAS												
Mean	8.61	9.00	5.14*	8.38	8.20	4.55	8.54	8.87	2.19	7.95	9.18	0.55
SD	3.02	2.23		3.22	3.12		3.02	2.43		3.30	3.18	
Animal naming												
Mean	9.70	10.45	4.62*	9.58	9.40	2.84	10.25	9.45	4.86*	9.35	9.45	0.23
SD	3.05	3.32		3.03	3.21		3.11	3.00		3.21	3.72	
Trails B												
Mean	5.16	6.16	1.64	4.72	2.42	5.17*	6.05	4.42	1.17	5.39	2.40	1.51
SD	3.88	3.86		3.47	0.53		4.32	2.97		3.97	0.54	
Digit span												
Mean	7.59	8.63	2.40	7.18	8.20	0.42	7.25	7.58	0.80	7.19	6.81	8.54*
SD	2.97	3.50		2.83	3.44		3.23	3.47		2.89	2.85	

* Significance $p \leq 0.05$. SD, standard deviation.

the extent of cognitive impairment. The fact that we did not take into account treatment status and duration of diabetes may partially explain our results. Other research has found that longer duration of diabetes is related to poorer cognitive performance [36]. Our sample is relatively young, and the duration of diabetes may mediate the lack of relationship found in our research.

The effects of dyslipidemia on cognitive function are not clear. A recent review of the relationship between plasma lipids, statins, and cognition concluded that the mechanisms for such a relationship are still not fully understood [12]. Our finding of no association among dyslipidemia and the extents of cognitive impairment is consistent with other studies that failed to find an association between lipid profiles and cognitive performance [37].

The effects of CVRFs on cognition has been extensively studied with conflicting results. Comorbidity is often not considered and even when other risk factors are controlled for, the possibility of confounding is real. In our study, we analyzed the comorbid effect of different combinations of two CVRFs. Despite the fact that diabetes and hypertension have been studied as the two risk factors with greater impact on cognition, literature about the additive effects of these CVRFs is sparse, especially among Mexican Americans. Unlike previous studies, which have not found a relationship between diabetes and hypertension and performance on measures of verbal fluency [28], we found that the co-occurrence of these CVRFs affected both language measures in our study. The physiological basis of this relationship is suggested by the work of Heinzel et al. [38], who found that individuals with CVRFs, specially hypertension, present a decreased functional hemodynamic response in the left inferior frontal junction, which is a region with the peak response during verbal fluency.

Despite many studies, the role of dyslipidemia in cognitive impairment in subjects with diabetes is not clear. In our cohort, the degree of executive function impairment was not influ-

enced by having a diagnosis of diabetes or dyslipidemia alone. However, the co-occurrence of these two risk factors negatively affected performance on Trails B, a measure of executive function. We also found that the comorbid effect of diabetes and obesity had a negative relationship with language and memory performance. These findings may be modulated by the presence of obesity. We can see again that previous research has studied risk factors in isolation, so future investigation of the additive effects of risk factors is granted.

This study had several limitations and strengths. A limitation of our study is the small sample size, and the cross-sectional design precludes any sort of causal inference. Longitudinal follow-up of the cohort will allow us to analyze changes in cognition through time and the prevalence of MCI conversions to Alzheimer's disease. Due to the majority of the sample being female, and its restriction to inclusion of only Mexican Americans, broad generalizability is not realistic. The ample age range in the sample may have directly impaired the outcomes. Because of the small sample size, we were not able to perform analysis using age sub-groups (e.g., younger vs. older). Studies of cognition that used this approach did find differences in the effect of CVRFs on cognition among different age groups [2]. Lastly, we did not analyze the impact of other potential CVRFs, and cofounders related to cognition like smoking, depression, and APOE ε4 allele, and data on medication use for hypertension, diabetes, and dyslipidemia were not included. Among the strengths of this study are a community-based sample, well-characterized MCI subjects, and using neuropsychological tests that have been normed for a Mexican American population. These facts give strength to our findings because the sample is likely a better reflection of the general Mexican American population, and the norms we used may be better indicators of actual levels of cognitive functioning than standard norms.

Conclusions

The current study provides additional evidence about the more intensive cognitive dysfunction in MCI subjects with CVRFs. We found that having obesity affects the degree of memory impairment. Furthermore, the study demonstrated that the MCI group with comorbid CVRFs showed a more distinct cognitive deficit in many areas, which may indicate a higher risk of developing dementia. Based on the results, it is likely that CVRFs not only increase the chance of having MCI, but also play a role in the intensity of the cognitive impairment. Mexican Americans suffer a greater burden of modifiable CVRFs such as hypertension, diabetes, obesity, and dyslipidemia, and are at increased risk of developing MCI and dementia. While the isolated risk factor effects on cognition have been explored in research, very few studies addressed the comorbid effect of these factors, especially in Mexican Americans. Further research on the cognitive effects of the accumulation of CVRFs on a larger sample size, and the longitudinal analysis of our cohort can lead to interventions for the effective control of these modifiable risk factors and to the reduction of cognitive impairment and dementia later in life.

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Statement of Ethics

This study has followed internationally accepted standards for research practice and reporting. Data collection was carried out in accordance with relevant guidelines and regulations and was approved by the North Texas Regional Institutional Review Board. All participants gave written informed consent for participation.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

All authors have read the paper and have agreed to be listed as authors. All authors agree with the manuscript results and conclusions. Conceived and designed the study: R.V., K.B., J.H., L.J., and S.O. Wrote the initial draft: R.V. and K.B. Acquisition of subjects/data: R.V. and L.J. Analysis and interpretation of data: J.H. and L.J. Preparation of manuscript: R.V. and K.B. Final review/editing of manuscript: S.O. and J.H.

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