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Risk factors for mild cognitive impairment among Mexican Americans

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Abstract

Background—While a great deal of literature has focused on risk factors for Mild Cognitive Impairment (MCI), little published work examines risk for MCI among Mexican Americans.

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Methods—Data from 1628 participants (non-Hispanic n= 1002; Mexican American n=626) were analyzed from two ongoing studies of cognitive aging and Alzheimer's disease, Project FRONTIER and TARCC.

Results—When looking at the full cohorts (non-Hispanic and Mexican American), age, education, APOE 4 status and gender were consistently related to MCI diagnosis across the two cohorts. However, when split by ethnicity advancing age was the only significant risk factor for MCI among Mexican Americans across both cohorts.

Conclusions—The current data suggests that many of the previously established risk factors for MCI among non-Hispanic cohorts may not be predictive of MCI among Mexican Americans and point to the need for additional work aimed at understanding factors related to cognitive aging among this underserved segment of the population.

Keywords

Mexican American; Mild Cognitive Impairment; cognition; Alzheimer's disease; ethnicity; cross-cultural; risk factors

1. Introduction

Mild Cognitive Impairment (MCI) is thought to reflect a transitional stage between normal cognitive aging and early dementia [1]. MCI patients demonstrate significant cognitive dysfunction in one or multiple cognitive domains, but retain the ability to manage their daily affairs (i.e. activities of daily living). It is estimated that between 10–30% of all adults age 65 and above suffer from MCI [2] with 10–15% of MCI patients progressing to Alzheimer's disease (AD) annually [1,3,4]. The recent working group from the National Institute on Aging and Alzheimer's Association provided revised diagnostic criteria for MCI due to Alzheimer's disease [5] which afforded the opportunity to utilize potential biomarkers (e.g. A neuroimaging, A in cerebrospinal fluid [CSF], tau in CSF) to identify which MCI patients likely suffer from underlying AD pathology.

There are many reasons for identifying risk factors for MCI, including generation of predictive tools for MCI/AD and identification of potentially modifiable mechanisms for reducing risk for MCI or slowing progression from MCI to AD. In fact, a sizable literature has accumulated showing that many of the primary factors related to AD are also significantly related to MCI risk, including age [6–8], education [7,8], gender [7,8], APOE 4 genotype [6,7], hypertension and heart disease [6,9,10], diabetes [11,12], and depression [6,12,13]. While there has been a surge in research over the last decade on the topic of MCI, there is a paucity of literature available on this construct among Hispanics residing within the U.S. [14]. The population of U.S. Hispanics ages 65 and above will *triple* by the year 2050 [15] with the rates of AD expected to grow six-fold [16]. Given that approximately 65% of the U.S. Hispanic population is Mexican American [17], this is the fastest aging segment of the population. Therefore, a tremendous need exists for research examining the construct of MCI, as well as dementia, among this underserved ethnic group [16, 18–20].

There is sufficient evidence to expect that MCI may differ among Mexican Americans as compared to non-Hispanics. The available AD/dementia literature suggests that Mexican Americans are diagnosed at more advanced stages of disease progression [19], are diagnosed at younger ages [19], are less likely to carry the APOE 4 allele [21], and suffer from a disproportionate burden of modifiable risk factors (e.g. diabetes, depression) [19,22]. The purpose of this study was to determine if the previously identified risk factors for MCI among non-Hispanic cohorts were applicable to Mexican Americans.

2. Methods

2.1 Participants

Data from 1628 participants (non-Hispanic $n=1002$; Mexican American $n=626$) were analyzed from two ongoing studies of cognitive aging and Alzheimer's disease, Project FRONTIER and TARCC.

Project FRONTIER (Facing Rural Obstacles to health Now Through Intervention, Education & Research)—Data from 509 participants (normal control [NC] $n=410$, MCI $n=99$) were analyzed. Project FRONTIER is a community-based epidemiological study of rural cognitive aging that utilizes a community-based participatory research (CBPR) approach. CBPR involves partnering communities with scientific groups to conduct studies of human disease. CBPR is particularly useful when working with underserved communities that may not respond to classic approaches (e.g., random digit dialing, mail surveys) and is supported by the National Institute of Environmental Health Sciences [23]. Partnerships were created with the local hospitals and clinics as well as other community (e.g. senior citizens' centers) organizations. Community recruiters and research personnel presented information about the study at community events, churches, food banks, as well as through door-to-door solicitation. Prior work from this study has demonstrated the comparability of the recruited cohort to that of the eligible population [24]. Inclusion criteria were (1) age 40 and above and (2) residing in one of the counties included in the study (Cochran, Bailey, or Parmer County, Texas).

TARCC (Texas Alzheimer's Research & Care Consortium)—Data from 1098 participants (NC= 774 ; MCI $n=325$) were analyzed. Participants completed a standardized examination at one of the five participating site (Texas Tech University Health Sciences Center, University of North Texas Health Science Center, University of Texas Southwestern Medical Center, University of Texas Health Science Center – San Antonio, and Baylor College of Medicine) dementia specialty clinics. Inclusion criteria for TARCC are age 50 or above with diagnosis of Probable AD [25], MCI [26] or normal control (NC) [27], Mini Mental State Exam (MMSE) score ≥ 11 (at entry), and available informant. Participants are excluded if their Hachinski Ischemic Score is greater than four; they have a history of stroke or have current cancer, neurological disease (e.g. Parkinson's disease), acute inflammatory disorders (multiple sclerosis, rheumatoid arthritis) or urinary infections. Data from both of these studies have been published extensively elsewhere [24, 28–36]. This research was conducted under IRB approved protocols with each participant (and/or informants for cognitively impaired persons) providing written informed consent.

2.2 Procedures

All participants underwent an examination that included a medical evaluation, neuropsychological testing, and interview according to a standardized protocol. Additionally, each participant provided blood for storage in the respective biobanks. The cognitive examination included the MMSE, Clinical Dementia Rating scale, as well as detailed neuropsychological testing (e.g. Wechsler Memory Scale Logical Memory and Visual Reproduction [TARCC only], CERAD List Learning and Memory [TARCC only], Trail Making Test, FAS, Animal Naming, Clock Drawing, Boston Naming Test, Repeatable Battery for the Assessment of Neuropsychological Status [RBANS, FRONTIER only], and Exit Interview [EXIT25, FRONTIER only]). Diagnoses were assigned according to standardized criteria for Mild Cognitive Impairment [26] or normal control [27] by consensus review consisting of physicians and neuropsychologists. Diagnosis of hypertension, hyperlipidemia, diabetes and current obesity were as follows: hyperlipidemia as defined by self-report OR use of cholesterol-lowering agents OR total serum cholesterol $>$

220mg/dL OR LDL > 140mg/dL; diabetes mellitus as defined by self-report OR history of treatment for diabetes with insulin or oral hypoglycemic agent OR fasting glucose > 126mg/dL; hypertension as defined by self-report OR use of antihypertensive medications OR documented systolic blood pressure > 140mmHg OR diastolic blood pressure > 90mmHg; body mass index (BMI; height [meters] and weight [kilograms]) as defined by BMI greater than or equal to 30. Depression was assessed using the Geriatric Depression Scale 30-item version [37]. Follow-up analyses were conducted using Project FRONTIER fasting clinical labs (HbA1c and triglycerides) and BMI values, which were not collected regularly as part of TARCC. Buffy coats were extracted from EDTA plasma collection tubes (purple top) for DNA extraction using Puregene® isolation kits. APOE ϵ 4 genotyping was conducted using standard polymerase chain reaction (PCR) methods [38]. A single fragment containing single nucleotide polymorphisms (SNPs) at nucleotides 112 and 158 (rs7412 and rs429358, respectively) of the APOE gene (which are diagnostic for APOE ϵ 4 genotype) were amplified from genomic DNA by PCR using Taq DNA polymerase (Roche Diagnostics; Indianapolis, IN) and a thermal profile, reaction conditions and primer sequences optimized for the locus. All amplifications were carried out in an ABI 7900HT thermal cycler (Applied Biosystems, Inc; Foster City, CA). Genotypes were determined by real-time PCR using custom TaqMan probes (Applied Biosystems, Inc) unique for each allele at each SNP. APOE genotype was defined from the combination of alleles present at the 112 and 158 polymorphisms.

2.3 Statistical analyses

Group comparisons were conducted via ANOVA (continuous) or χ^2 (categorical) analyses. A series of logistic regression analyses were conducted to examine the risk of MCI diagnosis (versus NC) as a function of the respective predictor variables: age, education, gender, GDS scores, APOE ϵ 4 presence, and presence (yes/no) of diabetes, hyperlipidemia, hypertension and obesity. Follow-up analyses using only Project FRONTIER data were conducted utilizing objective measures of HbA1c, triglycerides, and BMI scores.

3. Results

Descriptive statistics for the sample are presented in Table 1 and Table 2. Among the Project FRONTIER cohort, the Mexican American participants were significantly younger ($F[1,529]=95.8, p<0.001$), achieved significantly fewer years of education ($F[1,536]=379.4, p<0.001$), scored significantly worse on the MMSE ($F[1,526]=56.6, p<0.001$), had significantly higher HbA1c levels ($F[1,530]=21.2, p<0.001$), significantly higher BMI ($F[1,534]=18.8, p<0.001$) and higher GDS scores ($F[1,532]=27.9, p<0.001$) when compared to non-Hispanics. In terms of diagnostic categorization, Mexican Americans were more likely to have a diagnosis of diabetes ($\chi^2=21.3, p<0.001$) and be categorized as obese ($\chi^2=11.9, p=0.001$). In this community-based cohort, the prevalence of MCI diagnosis was 19% for non-Hispanics and 20% for Mexican Americans, which was not significantly different ($\chi^2=0.16, p>0.05$). See Table 1.

When examined by diagnostic category, Mexican American NC participants were significantly younger ($F[1,409]=70.9, p<0.001$), achieved significantly fewer years of education ($F[1,413]=334.3, p<0.001$), performed significantly worse on the MMSE ($F[1,414]=55.1, p<0.001$), had higher HbA1c levels ($F[1,410]=17.6, p<0.001$), higher BMI ($F[1,413]=8.9, p=0.003$), and higher GDS scores ($F[1,412]=17.8, p<0.001$) when compared to non-Hispanics. Mexican American NC participants were also more likely to have a diagnosis of diabetes ($\chi^2=13.6, p<0.001$) and be categorized as obese ($\chi^2=9.4, p=0.002$). Among the MCI participants, the Mexican American group was significantly younger ($F[1,98]=28.7, p<0.001$), achieved significantly fewer years of education ($F[1,99]=56.7,$

$p<0.001$), performed significantly worse on the MMSE ($F[1,97]=9.8$, $p=0.002$), and had higher BMI ($F[1,99]=12.5$, $p=0.001$) and GDS scores ($F[1,99]=6.7$, $p=0.01$). See Table 2.

Among the TARCC cohort, Mexican American participants were significantly younger ($F[1,979]=37.9$, $p<0.001$), achieved fewer years of education ($F[1,979]=152$, $p<0.001$), and scored worse on the MMSE ($F[1,979]=33.3$, $p<0.001$) as compared to non-Hispanics. Mexican Americans were more likely to have a diagnosis of hyperlipidemia ($\chi^2=11.4$, $p=0.003$), hypertension ($\chi^2=8.1$, $p=0.004$), diabetes ($\chi^2=72.5$, $p<0.001$) and be categorized as obese ($\chi^2=83.4$, $p<0.001$). As the TARCC is a clinic-based study with pre-defined goals by ethnicity and diagnosis, prevalence rates of diagnosis is not an appropriate calculation from this cohort. When broken down by diagnostic category, the Mexican American NC participants were significantly younger ($F[1,716]=52.8$, $p<0.001$), achieved significantly fewer years of education ($F[1,716]=102.6$, $p<0.001$), and scored significantly worse on the MMSE ($F[1,716]=58.0$, $p<0.001$) than non-Hispanic NC participants. Mexican American NC participants were more likely to have a diagnosis of diabetes ($\chi^2=53.3$, $p<0.001$) and be classified as obese ($\chi^2=72.8$, $p<0.001$) compared to non-Hispanics. Among the MCI sample, the Mexican American group achieved significantly fewer years of education ($F[1,261]=50.6$, $p<0.001$) and had significantly lower CDR Sum of Boxes scores ($F[1,715]=9.9$, $p=0.002$) when compared to the non-Hispanic sample. Mexican American MCI participants were more likely to have a diagnosis of diabetes ($\chi^2=53.3$, $p<0.001$) and be classified as obese ($\chi^2=72.8$, $p<0.001$). See Tables 1 and 2.

Next, a series of logistic regression models were generated entering the putative risk factors into a single step with diagnosis (MCI versus control) as the outcome variable. Table 3 presents the odds ratios (OR) for the total samples based on cohort. The factors significantly related to MCI status included age, gender, education, APOE ϵ_4 status, depression scores and diabetes presence (see Table 3).

The logistic regressions were then re-run split by ethnicity in both cohorts. Among the Project FRONTIER cohort, age, gender, education, hyperlipidemia diagnosis, diabetes diagnosis, and APOE ϵ_4 genotype were each significantly related to MCI risk for non-Hispanics (see Table 4). However, the only significant risk factor for MCI diagnosis among Mexican Americans in Project FRONTIER was age (OR=1.08, 95% CI=1.03–1.14)(see Table 4). Follow-up analyses utilizing objective measures related to the cardiovascular risk factors (rather than dichotomous yes/no) showed that HbA1c and BMI were significantly related to MCI risk among non-Hispanics whereas none of the variables (HbA1c, total triglycerides, BMI) were significantly related to MCI risk among Mexican Americans (see Table 5). When a summed cardiovascular/metabolic risk score (i.e. obesity + hypertension + hyperlipidemia + diabetes) was created and entered into the model, this new summed factor showed a trend towards significance among Mexican Americans (OR=1.32, 95% CI=0.92–1.89, $p=0.1$) though there was no such trend among non-Hispanics (OR=0.93, 95% CI=0.69–1.27, $p=0.67$). If this new metabolic factor was coded as having 0–1 factor present versus 2 or more, the link appeared stronger though still non-significant for Mexican Americans (OR=2.38, 95% CI=0.89–6.38, $p=0.08$) whereas there was no change among non-Hispanics.

Among the TARCC cohort, age, gender, education, and GDS scores were significantly related to MCI risk among non-Hispanics, which largely cross-validates findings from Project FRONTIER. Again cross-validating Project FRONTIER analyses, among Mexican Americans, age was a significant risk factor for MCI diagnosis (OR=1.16, 95% CI=1.10–1.22) whereas gender, education, APOE ϵ_4 genotype, and cardiovascular risk factor diagnosis were not significantly related to MCI diagnosis. Among TARCC participants, higher GDS scores were related to a significantly increased risk of MCI diagnosis

(OR=1.22, 95% CI= 1.13–1.31) (see Table 4) within the Mexican American sample. When a summed cardiovascular/metabolic risk score (i.e. obesity + hypertension + hyperlipidemia + diabetes) was created and entered into the model, this new summed factor showed a trend towards significance among Mexican Americans (OR=1.23, 95% CI=0.97–1.56, $p=0.09$) though there was no such trend among non-Hispanics (OR=1.03, 95% CI=0.87–1.21, $p=0.73$). These findings are similar to those found in the Project FRONTIER cohort. If this new metabolic factor was coded as having 0–1 factor present versus 2 or more, the link appeared stronger though still non-significant for Mexican Americans (OR=1.77, 95% CI=0.76–4.10, $p=0.1$) whereas there was no change among non-Hispanics.

4. Discussion

The current findings provide the first empirical investigation directly examining risk factors for MCI among Mexican Americans. Our findings highlight the need for substantial work on the topic among this rapidly growing segment of the aging population. The prevalence of MCI among a community-based cohort was 19% among non-Hispanics and 20% among Mexican Americans, which is similar to results found by others [8,12]. The only factor that consistently conveyed increased risk for MCI across these two cohorts was age, with the possibility of depression adding to MCI risk among Mexican Americans. Despite the fact that Mexican Americans (NC and MCI) expressed higher levels of diabetes, neither dichotomous disease presence nor HbA1c levels conveyed significant risk for MCI. None of the other cardiovascular risk factors increased risk for MCI.

A key finding of the current study is the significant age discrepancy between Mexican American and non-Hispanic MCI cases within the community-based cohort. We have previously shown that Mexican Americans/Hispanics appear to be diagnosed with dementia/AD and MCI at younger ages [19, 24]. This earlier age of onset extends to other conditions, such as diabetes. In the FRONTIER cohort, the average age of diabetes onset was 57 for non-Hispanics, but 48 among Mexican Americans though the average duration of diabetes was comparable between ethnicities (11 years for non-Hispanics and 10 for Mexican Americans). Therefore, Mexican Americans are suffering a disproportionate length of burden of illness/disease, which will likely have a significant impact on population aging though what this impact will be is not yet known. It is possible that this younger age is reflective of cognitive impairment due to other factors not fully investigated within this study and needs to be studied further. For example, it is possible that biases within the cognitive tests themselves (discussed in more detail below) impacted the diagnosis process. While possible, it is unlikely that such biases would only influence the age of diagnosis and not the overall diagnosis rates. However, as we have previously pointed out [24], it is also possible that the methodological practice of (1) enrolling individuals from clinic-based studies as well as (2) age requirements of 65 years or older for study enrollment have artificially skewed the age of MCI to older years. Because of the young age, analyses were also conducted examining the link between these same risk factors and neuropsychological domain scores (using the RBANS) among the community-based cohort. Age and education were the only consistently significant risk factors related to neuropsychological test performance among Mexican Americans (data not shown). This data and analyses are part of a separate ongoing study designed to present neuropsychological normative data for Mexican Americans (discussed below).

The fact that education did not convey a protective effect against MCI risk among Mexican Americans is of concern, but consistent with prior work. Cagney & Lauderdale [39] examined data from Wave 1 of the Asset and Health Dynamics Among the Oldest Old study and found that educational attainment was only significantly related to cognitive abilities (memory, working memory, knowledge/language/orientation) for educational ranges of 0–3

or 4–7, without any additional relation with advancing educational attainment. This is in stark contrast to non-Hispanic whites and Blacks who benefitted from educational attainment across the full range of educational categories (0–3, 4–7, 8–11, 12, 13–15, 16+). Of note, over 66% of the sample achieved less than 8 years of education. In order to examine this in more depth, the frequency of MCI diagnosis by educational categories (0–9yrs, 10–12yrs, 13+yrs) by ethnicity from the current cohorts was provided in Table 6. As can be seen from that data, there may be a threshold effect for protection against MCI diagnosis among Mexican Americans such that education does not offer a reduction in prevalence until 13 or more years have been achieved, while lower levels of education increases risk for MCI (see Table 6). Even then, the percent reduction may be less than observed among non-Hispanics based on our community-based cohort study. This possibility of a threshold effect was also identified in the Biologically Resilient Adults in Neurologic Studies (BRAiNS) project such that the protective effect of education against MCI was only for those achieving at least some college level of education [7]. The sample from the Cagney & Lauderdale study above, largely achieved educational levels less than high school and therefore also below a possible threshold for protection. The average education of Mexican Americans (NC and MCI) was significantly lower than that of the non-Hispanic samples across our cohorts, which is also consistent with educational trends within the U.S. Therefore, it appears possible that there were insufficient numbers of Mexican Americans reaching the threshold of 13 years of education for this variable to become a significantly protective factor for the group. When combining the aging nature of the Mexican American population with the lower average education of that population (and lack of protective effect of education), the incidence of MCI may increase disproportionately among this ethnic group over the next several decades as it is too late to increase educational attainment among those Mexican Americans now at risk for incident MCI. Another construct that has been studied extensively among African Americans is the notion of quality of education [40]. Additionally, we and others have found that self-reported level of education is oftentimes higher than estimated reading level among African Americans [41, 42] though this has received less attention when studying Hispanic populations. It is certainly possible that quality of education, location of education, and other education-related factors are important and need to be examined in more detail among U.S. Mexican Americans.

While cardiovascular/metabolic factors have been associated with MCI, results have not always been consistent [43, 44] and the risk associated with these various factors (including APOE 4 genotype) has been shown to vary by age, gender, and ethnicity [8, 45–48]. Therefore, additional work is needed to clarify risk factors for MCI by specific populations. Prior work has shown diabetes to be more common among Mexican Americans [40,41] and others have suggested that diabetes may be a driving factor for AD among this ethnic group [21], therefore it may be advantageous to specifically examine the diabetes – MCI/AD link among Mexican Americans. In fact, diabetes was more prevalent among Mexican Americans in both cohorts across normal controls and MCI cases. Despite the increased prevalence of diabetes, this was not a risk factor for MCI diagnosis among Mexican Americans. Additionally, when HbA1c levels were examined among the Project FRONTIER cohort, this was a significant predictor of MCI diagnosis among non-Hispanics, but was not related to MCI designation among Mexican Americans. In Project FRONTIER, years of diabetes diagnosis was not significantly related to MCI diagnosis among either ethnic group (data not shown). Roberts et al [42] analyzed data from 329 MCI individuals from Olmsted County (Minnesota) and found MCI diagnosis to be related to earlier onset, longer duration, and greater severity of diabetes. Our results are conflicting with those findings and require further investigation. It is possible that diabetes presence/absence and HbA1c levels are inadequate variables for studying this link. As has been pointed out previously, it is possible that it the culmination of multiple metabolic/cardiovascular factors

is more important than any individual factor alone [49, 53]. In fact, when a summed score of presence/absence of these factors was created, this summary score showed a trend towards being a significant risk factor for MCI among Mexican Americans, but not among non-Hispanics, which was consistent across cohorts. This concept of a metabolic endophenotype among Mexican Americans is consistent with other biomarker work from our laboratory as a blood-based biomarker profile of AD showed a preponderance of metabolic-related factors that was different from the non-Hispanic AD biomarker profile we have previously published (O'Bryant et al manuscripts under review for publication). Therefore, the current group is now looking further into the identification of a metabolic endophenotype of cognitive dysfunction/MCI/AD that incorporates blood-based biomarkers and clinical labs among Mexican Americans.

APOE 4 genotype only conveyed increased risk for MCI among non-Hispanics. Additionally, APOE 4 was less frequency among Mexican Americans, which is similar to prior work [21]. This data does not suggest that APOE 4 has no mechanistic impact on risk for MCI, but rather that the allele is too infrequent to convey significant risk at the group level. It is noteworthy that the odds ratio (OR) for risk of MCI conveyed by presence of the APOE 4 genotype was comparable in our study to that found by others [8, 47, 54] suggesting sample size to be another factor when interpreting this finding. On the other hand, the less frequent APOE 4 but comparable MCI (current data) and AD [21] prevalence rates suggests other factors need to be identified in order to better understand biological mechanisms of cognitive decline among Mexican Americans if targeted preventative therapies are to be generated. Jun and colleagues [55] conducted a meta-analysis of genome-wide allelic association study (GWAS) data from several large-scale cohorts that included over 500 Caribbean Hispanics AD cases. They confirmed the link between AD and APOE 4 genotype among all ethnic groups, including Hispanics; however, other genetic markers commonly associated with AD status in prior studies (CLU, CR1 and PICALM) were associated with AD status among non-Hispanic whites but not any other ethnic group (African American, Israeli-Arab, or Hispanic). Bertoli Avella and colleagues [56] identified a novel presenilin 1 mutation (L174 M) that was associated with early onset AD among a large Cuban family. If one looks at the genetics of fatty acid binding protein (FABP), small intracellular cytoplasmic proteins involved in binding and transporting fatty acids, which has been associated with many metabolic/cardiovascular factors, ethnic variation has been found [57]. For example, the Ala54Thr FABP2 polymorphism was specifically associated with type 2 diabetes (T2DM) among Hispanic Americans [58], and a new SNP of FABP5 (rs454550) specifically associated with T2DM among non-Hispanic whites and African Americans [58]. Therefore, there is a great need to study the biology of MCI/AD among Mexican Americans specifically.

In the TARCC cohort, greater symptoms of depression conveyed an increased risk for MCI diagnosis; however, these findings were not generalizable to the FRONTIER cohort. However, our prior work has shown that particular depressive symptom clusters are of more importance when considering the depression – cognition link [28,36]. Current work is underway to determine if specific depressive symptom clusters differentially impact risk for MCI diagnosis and if these patterns vary according to Mexican American ethnicity. The data presented here suggests that Mexican American elders experience higher levels of depression, which is consistent with our prior work [19]. If depression is confirmed as a significant risk factor for MCI among Mexican Americans, this may offer a potential preventative entry point for halting or delaying progression to AD.

There are limitations to the current study. The cross-sectional nature prevents any causative conclusions as well as identifying risk for incident MCI. However, the TARCC cohort is being followed longitudinally and risk factors for MCI incidence (rather than prevalence)

will be examined as that project matures. Additionally, the current investigative team has begun a new longitudinal study of cognitive aging among Latino elders (primarily Mexican American) entitled the Health & Aging Brain among Latino Elders (HABLE) study. This study will investigate a wide range of lifestyle factors (e.g. diet, physical activity, leisure activity) as well as biological risk factors for MCI among Mexican Americans in an effort to provide sufficient support for targeted prevention trials. Another potential limitation is the possibility of cognitive test bias. That is, if the neuropsychological tests utilized within the study were biased against Mexican Americans, this bias could have influenced the diagnostic process, which in turn could impact the makeup of the MCI groups by ethnic groupings. The current research team has generated the Texas Mexican American Normative Studies (TMANS), which is designed to provide normative data specifically for Mexican American adults and elders (manuscripts in preparation). Interestingly, within that series of studies, it has been found that education is the primary demographic factor related to nearly all neuropsychological test scores with age, gender, education and language of test administration rarely accounting for clinically significant amounts of variance within test scores (i.e. 10% or greater). As can be seen from Table 6 below, low levels of education increase risk for MCI diagnosis across ethnic groups whereas higher levels reduce that risk though the reduction was not significant among the Mexican American cohort (as discussed above). Therefore, additional work is needed to better understand the cognitive testing constructs themselves across ethnically diverse cohorts to ensure that studies examining cognitive dysfunction/decline are accurately testing the proposed hypotheses. The TMANS projects will facilitate that process. While the overall sample size of the study, and the overall number of MCI cases of Mexican American ethnicity, is larger than most previously conducted work, the sample size is still less than optimal. It is also possible that years of residence within the U.S. play a role in risk for MCI. This relates to the concept of acculturation and should be studied within this context, which the group is looking into but such data does not exist for TARCC or FRONTIER. It is also possible that the high prevalence rates of the metabolic/cardiovascular factors may have reduced the capacity to differentiate based on the factors themselves. However, such prevalence rates may make these cohorts uniquely suited to study the mechanistic links between these factors and MCI/AD, which the investigative team is undertaking. On the other hand, the current study is unique in that it (1) identifies differential risk factors for MCI and (2) cross-validates these findings across independent cohorts. An additional unique aspect to this project is that findings are cross-validated across clinic-based and community-based samples.

The current findings question the applicability and relevance of the existing literature on risk factors for MCI for Mexican Americans. In fact, the only consistently significant risk across ethnicities was age. In light of (1) the rapidly growing elderly Mexican American population and (2) the significantly younger age of onset of MCI among Mexican Americans, there is a tremendous need for additional work on this topic.

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Table 1

Demographic characteristics by cohort

	TARCC		FRONTIER	
	Mexican American (n=409)*	Non-Hispanic (n=689)*	Mexican American (n=217)*	Non-Hispanic (n=313)*
Age (years)	68.1(8.3) 50–92	71.7(9.0) 52–94	55.5(10.3) 40–86	65.5(12.7) 40–96
Education (years)	12.1(4.2) 0–20	15.2(2.6) 6–23	7.4(4.1) 0–18	13.2(2.7) 2–20
Gender (% male)	38%	38%	30%	31%
Hypertension (%yes)	66%	58%	59%	58%
Hyperlipidemia (%yes)	63%	56%	58%	63%
Diabetes (%yes)	35%	12%	40%	22%
Obese(%yes)	51%	23%	49%	34%
GDS score	5.5(5.5) 0–28	4.1(4.2) 0–26	11.9(5.5) 0–26	9.6(4.5) 0–22
APOE 4 (% positive)	19%	29%	22%	25%
MMSE score	27.9(2.3) 19–30	28.8(1.6) 19–30	26.6(3.2) 14–30	28.2(2.2) 12–30
CDR SB	0.3(0.5) 0–3.0	0.4(0.8) 0–5.0	0.3(0.7) 0–5.0	0.3(0.7) 0–5.0

NOTE: BP=blood pressure, BMI = body mass index;

* where appropriate, mean (standard deviation) and range are presented

Table 2

MCI and normal control characteristics by cohort

	TARCC		FRONTIER	
Normal Controls	N=281*	N=493*	N=165*	N=245*
	Mexican American	Non-Hispanic	Mexican American	Non-Hispanic
Age (years)	66.0(7.6) 50–87	70.9(9.0) 52–93	54.2(9.2) 40–83	63.7(12.4) 40–96
Education (years)	12.4(4.2) 0–20	15.5(2.6) 8–23	7.7(4.0) 0–18	13.7(2.6) 6–20
Gender (% male)	37%	35%	26%	32%
Hypertension (%yes)	63%	57%	57%	53%
Hyperlipidemia (%yes)	62%	54%	57%	65%
Diabetes (%yes)	35%	11%	35%	19%
Obese(%yes)	54%	21%	52%	37%
GDS score	4.2(4.3) 0–27	3.3(3.4) 0–22	11.5(5.5) 0–26	9.4(4.2) 0–22
APOE 4 (% positive)	18%	27%	22%	22%
MMSE score	28.4(2.1) 19–30	29.3(0.9) 25–30	27.3(2.6) 19–30	28.8(1.5) 22–30
CDR SB	0.01(0.2) 0–3	0.01(0.09) 0–1	0.2(0.5) 0–4	0.2(0.4) 0–5
Mild Cognitive Impairment	N=128	N=197	N=41	N=58
Age	72.7(8.1) 53–92	73.6(8.7) 54–94	60.4(11.1) 40–82	72.6(11.1) 47–94
Education	11.4(4.1) 0–20	14.7(2.5) 6–20	6.6(4.3) 0–15	11.7(2.3) 2–18
Gender (% male)	41%	47%	44%	26%
Hypertension (%yes)	76%	63%	67%	78%
Hyperlipidemia (%yes)	69%	59%	65%	50%
Diabetes (%yes)	34%	15%	56%	31%
Obese(%yes)	46%	27%	43%	26%
GDS score	8.4(6.6) 0–27	5.8(5.0) 0–26	12.2(5.4) 0–20	9.4(5.5) 0–21
APOE 4 (% positive)	24%	35%	23%	33%
MMSE score	26.8(2.4) 20–30	27.5(2.3) 19–30	24.5(3.6) 17–30	26.4(2.4) 20–30
CDR SB	1.0(0.6) 1–3	1.3(0.9) 1–5	0.7(0.9) 0–4	0.9(0.8) 0–4

NOTE:

* where appropriate, mean (standard deviation) and range are presented

Table 3

Odds ratios (95% CI) for MCI risk by cohort

	TARCC	FRONTIER
	Odds Ratio(95% CI)	Odds Ratio(95% CI)
Age	1.07(1.05–1.10); p<0.001	1.06(1.04–1.08); p<0.001
Gender	0.60(0.41–.089); p=0.007	1.20(.069–2.09); p=0.54
Education	0.92(0.86–0.98); p=0.007	0.92(0.87–0.97); p=0.05
Hypertension	0.98(0.66–1.46); p=0.92	1.65(0.93–2.93); p=0.09
Hyperlipidemia	1.17(0.01–1.50); p=0.24	0.60(0.35–1.02); p=0.25
Diabetes	1.13(0.71–1.78); p=0.61	1.99(1.12–3.52); p=0.02
Obesity	1.05(0.81–1.36); p=0.73	0.63(0.36–1.11); p=0.11
GDS score	1.18(1.13–1.23); p<0.001	1.04(0.98–1.09); p=0.20
APOE 4	1.56(1.04–2.33); p=0.03	1.88(1.06–3.33); p=0.03

NOTE: CI=confidence interval; GDS=Geriatric Depression Scale

Table 4

Odds ratios for potential MCI risk factors by cohort

	TARCC Odds Ratio(95% CI)		FRONTIER Odds Ratio (95% CI)	
	Mexican American	Non-Hispanic	Mexican American	Non-Hispanic
Age	1.16(1.10–1.22); p<0.001	1.04(1.02–1.07); p=0.002	1.08(1.03–1.14); p=0.002	1.06(1.03–1.09); p=0.001
Gender	0.56(0.28–1.11); p=0.10	0.56(0.35–.090); p=0.017	0.53(0.23–1.23); p=0.15	2.55(1.09–6.07); p=0.03
Education	1.01(0.88–1.16); p=0.87	0.87(0.79–0.95); p=0.003	1.04(0.93–1.18); p=0.49	0.74(0.62–0.88); p<0.001
Hypertension	1.68(0.77–3.68); p=0.19	0.67(0.40–1.12); p=0.14	1.37(0.57–3.27); p=0.49	1.79(0.79–4.06); p=0.17
Hyperlipidemia	1.05(0.67–1.67); p=0.82	1.23(0.87–1.71); p=0.26	1.10(0.47–2.55); p=0.83	0.40(0.19–0.83); p=0.02
Diabetes	1.70(0.83–3.48); p=0.15	0.92(0.45–1.85); p=0.80	1.84(0.81–4.19); p=0.14	2.53(1.05–6.01); p=0.04
Obesity	0.91(0.45–1.85); p=0.79	1.07(0.82–1.40); p=0.63	0.98(0.43–2.22); p=0.96	0.47(0.19–1.13); p=0.10
GDS score	1.22(1.13–1.31); p<0.001	1.17(1.11–1.24); p<0.001	1.05(0.97–1.13); p=0.25	1.05(0.97–1.14); p=0.19
APOE 4	1.89(0.83–4.34); p=0.13	1.43(0.88–2.30); p=0.15	1.53(0.60–3.90); p=0.38	2.58(1.05–6.07); p=0.02

NOTE: OR=odds ratio; CI=confidence interval; GDS=Geriatric Depression Scale

Table 5

Odds ratios for potential MCI risk factors in FRONTIER- Objective measures

	Mexican American		Non-Hispanic	
	Mean (SD) Range	Odds Ratio (95% CI)	Mean (SD) Range	Odds Ratio (95% CI)
HbA1c	6.4(1.7) 4.6–14	1.15(0.95–1.40); p=0.16	5.9(1.0) 4.1–14.0	1.51(1.16–1.96); p=0.002
Triglycerides	174.1(129.8) 39–1150	1.00(0.99–1.00); p=0.55	158.1(117.1) 38–1176	1.00(0.97–1.01); p=0.83
BMI	30.9(6.1) 18.5–65.6	1.02(0.95–1.40); p=0.40	28.6(6.0) 11.8–61.1	0.92(0.86–0.98); p=0.007

NOTE: CI=confidence intervals

Table 6

Percent MCI diagnoses by educational ranges

	TARCC		FRONTIER	
	Mexican American	Non-Hispanic	Mexican American	Non-Hispanic
0–9yrs	38%	50% *	21%	38%
10–12yrs	36%	37%	22%	30%
13+yrs	25%	26%	13%	8%

NOTE:

* only 2 non-Hispanics in TARCC completed only 0–9yrs education.