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Younger age of dementia diagnosis in a Hispanic population in southern California

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Abstract

Objective—Prior studies of U.S. Hispanics, largely performed on the east coast, have found a younger age of dementia onset than in white non-Hispanics. We performed a cross-sectional study to examine clinical and socio-demographic variables associated with age of dementia diagnosis in aged Hispanics and white, non-Hispanics in southern California.

Methods—Two hundred ninety (110 Hispanic and 180 white non-Hispanic) community dwelling, cognitively symptomatic subjects, age 50 years and older, were assessed and diagnosed with probable Alzheimer's disease or probable vascular dementia. Apolipoprotein E genotype (APOE) was assessed in a subset of cases. Analysis of variance and multiple stepwise linear regression were used to assess main effects and interactions of ethnicity with dementia severity (indexed by Mini-Mental Status Exam scores) and other socio-demographic and clinical variables on age of dementia diagnosis.

Results—Hispanics were younger by an average of 4 years at the time of diagnosis, regardless of dementia subtype, despite a similar prevalence of the APOE ε4 genotype. The earlier age at diagnosis for Hispanics was not explained by gender, dementia severity, years of education, history of hypercholesterolemia, hypertension, or diabetes. Only ethnicity was significantly associated with age of onset.

Conclusions—These findings confirm that U.S. Hispanics living in the southwestern U.S. tend to be younger at the time of dementia diagnosis than their white non-Hispanic counterparts. As this is not explained by presence of the APOE ε4 genotype, further studies should explore other cultural, medical or genetic risk factors influencing the age of dementia onset in this population.

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Keywords

Age; diagnosis; onset; Hispanic; Latino; Dementia; Alzheimer's disease; APOE genotype; diagnosis; vascular dementia

Introduction

Older Hispanic adults are the most rapidly expanding group of aged persons in California and the United States (www.census.gov/population/hispanic/data/2011.html). (He et al., 2005). By 2020 they will comprise over 20% of aged Californians, the state with the highest density of Hispanics. Numerous other states will undergo similar changes. Persons of Puerto Rican origin comprise 38% of the Hispanic population in the northeastern U.S., where most dementia research in U.S. Hispanics has been performed, with Dominicans and other persons of Caribbean origin being well-represented. Persons of Mexican descent make up only 13% of the Hispanic population in the northeast though comprise 81% of Hispanics in the west. Hispanics in the eastern U.S. therefore have different geographical origins, racial admixtures, and customs than their western counterparts and one cannot assume that observations made in one population will generalize to another.

Diabetes, hypertension, dyslipidemia, and cerebrovascular disease are more prevalent among older Hispanics than among older white non-Hispanics(Harris, 2001, Singh and Deedwania, 2006) (Umpierrez et al., 2007, Sacco et al., 1998, Shepardson et al., 2011) and have been found to increase the risk for dementia and accelerate cognitive decline in persons with dementia(Crane et al., 2013, Mayeda et al., 2013) (Shepardson et al., 2011). However, relatively few studies have explored the clinical and socio-demographic characteristics of Hispanics with dementia in the western U.S. compared to other ethnic groups.

The purpose of this study was to assess the impact of clinical and socio-demographic variables on age of diagnosis of Alzheimer's disease (AD) and vascular dementia (VaD) in a sample of Hispanics and white non-Hispanics living in southern California.

Methods

The study included subjects followed in the University of California at Los Angeles AD Research Center (UCLA ADRC) between 1998 and 2005. Hispanic and white non-Hispanic subjects were enrolled at two sites: the ADRC at the UCLA Medical Center in Westwood and the Olive View Medical Center (OVMC). The UCLA Medical Center serves central and western Los Angeles and has an estimated ethnic composition of 76% white non-Hispanic, 18% Hispanic, 11% Asian-Pacific Islander, and 5% African American while the OVMC is a public hospital serving an under- or uninsured population comprised of 56% Hispanics, 33% white non-Hispanics, 5.4% Asian-Pacific Islanders, 5% African Americans, and 0.4% persons of other origin.

Subjects

Hispanic and white non-Hispanic subjects were recruited for dementia evaluations either from clinic referrals or from the community. Recruitment methods developed at the UCLA

ADRC included educational presentations conducted in both Spanish and English at churches or synagogues, senior centers, and social service agencies. Also used were radio advertisements, bilingual community flyers, presentations to primary healthcare professionals and articles published in local newspapers.

During the study, a total of 553 subjects at UCLA and 318 subjects at the Olive View-UCLA Medical Center were screened. Hispanic subjects were identified, recruited, and evaluated by natively Spanish-speaking clinical staff. Ethnicity of subjects was documented by investigators through the use of subject self-report and further confirmed through relative identification, place of birth, ancestry, surname and language.

Study inclusion criteria required the diagnosis of probable AD or probable VaD without a previous diagnosis of these conditions. Dementia cases due to other etiologies were excluded. Subjects aged 50 years or older who had complete medical and medication histories were included. Two hundred and ninety subjects met all study criteria and were enrolled in the study: 180 were white non-Hispanics and 110 were Hispanics. Apolipoprotein E genotype was available for 25 of the 180 non-Hispanic cases, and for 43 of the 110 Hispanic cases.

Assessments

Subjects at both sites were evaluated using a standard protocol. Identical criteria for enrollment were used for both sites and informed consent was obtained from all subjects in their native language.

All enrolled subjects received the UCLA ADRC diagnostic battery which includes a complete medical and functional history, neurological exam, mental status examination including the Mini-Mental Status Exam (MMSE)(Folstein et al., 1975) and comprehensive neuropsychological assessment in their native language. A Spanish-language version of the MMSE with concurrent validity was used to evaluate cognitive symptoms in the Hispanic group(Taussig et al., 1996). MMSE scores were adjusted for age and education as per Mungas et al (MMSAdj = Raw MMS - (0.471 X [Education-12]) + (0.131 X [Age-70]) (Mungas et al., 1996). The neuropsychological battery used for Spanish-speaking subjects was normed and standardized for Hispanics in Southern California(Ponton et al., 1996) The assessment also included blood pressure measurement, review of systems, medication history, and magnetic resonance imaging or computed tomography of the brain as indicated. Apolipoprotein E (APOE) genotyping was not uniformly available over the time period of this study and, when available, was an optional part of the study design. Therefore, only a subset of consenting participants underwent such genotyping. All cases were reviewed by a multi-disciplinary team in a consensus conference. The team variably included a research nurse, neurologists, geriatric psychiatrists, geriatrician, neuropsychologists and psychometricians. At least a medical doctor, research associate, and psychometrician contributed to the diagnosis of each case. All rating clinicians attended case-based inter-rater reliability training sessions prior to and at several intervals during the course of the study to maintain diagnostic consistency.

At the consensus conference, subjects were classified as having either no cognitive impairment, having impairment not sufficient for a dementia diagnosis, or having dementia. Age of dementia diagnosis was defined as the age at which the first assessment occurred in which a diagnosis of dementia was rendered. Subjects having dementia diagnoses prior to their evaluation in the current study were excluded. If a diagnosis of dementia was assigned, a consensus for the etiology was sought. This protocol was reviewed and approved by Institutional Review Boards at both sites and all subjects, or their proxies, signed informed consent.

The presence of dementia was established according to the DSM-IV criteria(1994). Diagnosis of probable AD was established using the NINDS-ADRDA criteria(McKhann et al., 1984). Diagnosis of probable vascular dementia (VaD) was based on the research criteria for probable VaD from the NINDS-AIREN(Roman et al., 1993). Subjects were identified as having or not having diabetes mellitus, hypertension, or hypercholesterolemia based on blood pressure measurements, medical histories and medication records.

Data Analysis

Comparisons of the two study populations with regard to age, gender, MMSE score, years of education, dementia diagnosis (AD vs. VaD) and presence of the APOE ε4 allele were conducted using t-tests for independent groups for continuous measures, and continuity-corrected χ^2 test of independence for categorical variables. Analysis of variance and multiple stepwise linear regression were used to assess main effects and interactions of ethnicity with other socio-demographic and clinical variables on age of dementia diagnosis. Statistical analyses were performed using the Statistical Package for the Social Sciences version 9.0 for IBM.

Results

Table 1 shows the socio-demographic and clinical characteristics of subjects from the two populations. The two groups did not differ in gender distribution, but Hispanics had significantly fewer years of education (6.3 vs. 12.6, t=12.4, df=288, $p < 0.001$) than did white non-Hispanics. The age range for both the Hispanic and white non-Hispanic groups was 50 to 94. Forty-seven percent of the Hispanic population identified themselves as being of Mexican origin, while 25% were of Central American, 15% South American, 7% Cuban, 4% Puerto Rican, and 2% of other origins.

Twenty-eight percent of Hispanics and 10.6% of the white non-Hispanics had a history of diabetes mellitus type II (28% vs. 11%, $\chi^2 = 13.2$, df = 1, $p < 0.001$). The Hispanic group also had higher rates of hypertension (59%) and hypercholesterolemia (35%) than the white non-Hispanic group (49% and 28% respectively) though the differences did not reach statistical significance. For the white non-Hispanic demented group, 9.4% (17/180) were age 65 or younger, whereas 23.6% (26/110) of the demented Hispanics were aged 65 or younger ($p < 0.001$).

The Hispanic cases had significantly lower MMSE scores at the time of diagnosis (15.2 vs. 19.3, t = 5.1, df = 288, $p < 0.001$) and slightly but significantly lower scores after adjustment

for age and education (17.8 vs. 19.7, t = 2.5, df = 288, $p < 0.01$). While probable AD was the predominant diagnosis for both groups, the Hispanic group had a significantly higher frequency of VaD compared to the white non-Hispanics (27% vs. 12%, $\chi^2 = 11.5$, df = 1, $p < 0.01$). The frequency of the *APOE* ε4 genotype, though lower in Hispanics, did not differ significantly between the Hispanic (12/43 or 28%) and non-Hispanic cases (12/25 or 48%, χ^2, p = 0.35).

Comparison of age at dementia diagnosis between the two populations revealed that Hispanics were diagnosed with dementia at a younger age than their white non-Hispanic counterparts, Hispanics being on average four years younger at the time of diagnosis (72.1 vs. 76.4, t = 4.1, df = 288, $p < 0.001$). Several analyses were run to determine if this age effect could be explained by differences in severity of illness or by other socio-demographic differences between the two populations. Figure 1 shows that the Hispanic sample was younger than the white non-Hispanic sample at all levels of impairment as indexed by MMSE scores. A two-way analysis of variance of age at diagnosis by ethnicity and MMSE severity level supported significant effects of both ethnicity (F = 17.6, df = 1,274, $p < 0.001$) and severity (F = 3.8, df = 3,274, $p < 0.01$) but no significant interaction between the two. This indicates that the difference in age at diagnosis between Hispanics and white non-Hispanics cannot be explained solely by differences in dementia severity.

Figure 2 shows the mean age at diagnosis by dementia type (AD, VaD) and ethnic population. The Hispanic sample was significantly younger than the white non-Hispanics, regardless of diagnosis (F = 11.1, df =1, 286, $p < 0.001$). There was no significant main effect or interaction of dementia type on age at diagnosis.

The effect of gender on age of dementia diagnosis in the two ethnic groups is shown in Figure 3. Males were significantly younger than females at initial diagnosis (F = 6.2, df = 1,286, p = 0.01), but the earlier age of diagnosis for the Hispanic sample held independent of gender (F = 14.2, df =1,286, $p < 0.001$). Years of education did not have a significant effect on diagnosis age in this sample, and including education as a covariate in the analysis did not alter the effect of ethnicity on diagnosis age (F = 15.38, df = 1,287, $p < 0.001$).

A stepwise linear regression was run to identify independent effects of relevant variables on age at diagnosis. Each of the potential confounding variables was forced into the equation prior to entering ethnicity. The results presented in Table 2 show independent effects only of gender and ethnicity on age of dementia diagnosis. The earlier age at diagnoses for the Hispanic patients could not be explained by gender, MMSE score, years of education, or history of hypercholesterolemia, hypertension, or diabetes.

Discussion

Results from this study suggest that age at the time of dementia onset is younger in Hispanics of Mexican and Central American origin living in Southern California than in white, non-Hispanics in the same area. Whereas education levels varied markedly between the study's Hispanic and non-Hispanic cohorts, the age effect was maintained when controlling for education, dementia severity, and history of hypercholesterolemia,

hypertension, or diabetes. Although the difference in APOE ε4 allele frequency between the two groups did not reach statistical significance, possibly as a result of the relatively small number of cases for which APOE results were available, the APOE ε4 allele was less common in Hispanics than in non-Hispanics, suggesting that other genetic or possibly reversible environmental dementia risk factors may contribute to a greater extent in the Hispanic population than in their non-Hispanic white counterparts.

Multiple studies (Livney et al., 2011, Clark et al., 2005, Gurland et al., 1999, Tang et al., 2001) using varied methodologies have suggested that Hispanics from both eastern and western U.S. regions may be at greater risk for developing dementia at an earlier age than white non-Hispanics. Gurland et al, (Gurland et al., 1999) in a study comparing three ethno-racial groups consisting of east coast Hispanics, African-Americans and white non-Hispanics, found Hispanics to have the greater prevalence rates of dementia in every stratified age group. However, in contrast to the present study, Gurland, et al. suggested that the lower rates in white non-Hispanics could be explained by better education and higher income levels. The results of the current study, together with other studies(Clark et al., 2005, Tang et al., 2001) have not provided strong support for this assertion. Tang, et al, (Tang et al., 2001) comparing three groups of age-stratified east coast Hispanic, African American and white non-Hispanic subjects with AD, found that the prevalence and incidence rate of newly acquired AD diagnoses were consistently higher in Caribbean Hispanics and African Americans, including in the youngest age stratum, 65 to 74, when compared to white non-Hispanics. This study further found that the difference in incidence rates in these three ethnic groups could not be explained by differences in education level, illiteracy or medical comorbidities. Clark, et al (Clark et al., 2005), also compared the age at AD symptom onset in a population consisting of both east and west coast Hispanics (N = 119) and white non-Hispanics (n = 55), recruited through five AD Centers. They found that Hispanics had a mean age at symptom onset 6.8 years younger than white non-Hispanics, even after controlling for MMSE, education and other socio-demographic factors.

AD is a multifactorial disease that, in addition to genetic risk factors such as APOE ε4 and others, includes multiple potentially modifiable risk factors such as hypertension, diabetes, obesity, depression, education level, etc(Barnes and Yaffe, 2011). Modifiable risk factors have been shown to accelerate cognitive aging(Yaffe et al., 2012, Craft et al., 2012, Whitmer et al., 2008) and may account for as many as half of all AD cases in the general population(Barnes and Yaffe, 2011). It is well established that older Hispanics have a higher prevalence of diabetes and other cardiovascular risk factors(Sanchez-Castillo et al., 2005) appearing at an earlier age(Haffner et al., 1991). In addition, older U.S. Hispanics are more likely to have suboptimal management of diabetes and other vascular risk factors(Kuo et al., 2003). Some studies(Luchsinger et al., 2001, Haan et al., 2003) have suggested that Mexican-Americans and other Caribbean Hispanic-Americans (except Cuban-Americans) have a higher risk of dementia and cognitive impairment attributed to diabetes than white non-Hispanic populations. In the present study, a history of diabetes in particular, but also of hypertension and elevated cholesterol, was higher in Hispanics though did not significantly influence the age of dementia onset. However, the severity, duration, and how these conditions were medically managed were not characterized in the current study and therefore whether modifying them might influence the age of onset could not be addressed.

In a study of California Hispanics, Haan, et al(Haan et al., 2003) found the prevalence of AD and VaD to be similar to that reported in other Canadian and European studies. A prevalence study of dementia in a community sample of older Hispanics(Fitten et al., 2001) found the number of cases with vascular dementia in Hispanics to be unexpectedly high. In the present study, AD was the predominant diagnosis for both groups, however the Hispanic group had a significantly higher incidence of vascular dementia.

For white non-Hispanics and African-Americans, APOE ε4 genotype is a significant risk factor for the development of AD and may be responsible for an earlier age of disease onset(Reitz et al., 2013). For aged Hispanics in the U.S., the nature of the association between AD and APOE genotype is incompletely characterized. Older Hispanics in the U.S. are a heterogeneous group with different ancestries predominantly influenced by a three-way admixture, in various proportions, of Native American, European, and West African populations. Tang, et al.(Tang et al., 1998), found that Caribbean Hispanics have an increased frequency of AD compared to white non-Hispanics, regardless of APOE genotype. Several other studies(Kwon et al., 2010, Olarte et al., 2006, Sevush et al., 2000, Villalpando-Berumen et al., 2008) suggest that the risk for early onset of AD associated with APOE ε4 genotype is significantly lower in older Mexicans and Caribbean Hispanics compared to white non-Hispanics. Haan, et al.(Haan et al., 2003) suggested that for older Hispanics the frequency of APOE ε4 genotype may decline with age as a result of differential population selection. The present study found that the white non-Hispanic group was consistently older and modestly, but not statistically significantly more likely to have one or more copies of the APOE ε4 allele (48% of cases) compared to the Hispanic group (28% of cases). These findings suggest that other, as yet unidentified genetic or biopsychosocial risk factors possibly related to diet, life style, or immigrant status may contribute to the younger age at time of dementia diagnosis in this population.

In southern California, we have identified many Mexican-Americans with AD of young onset due to autosomal dominantly inherited familial AD (FAD). An overrepresentation of such persons in the current Hispanic sample could explain our findings. However, only one Hispanic in the current study had a family history suggestive of FAD and was subsequently found to harbor an APP mutation. Though it is possible there were other persons with FAD in our cohort who were not known to carry such mutations, such an occurrence is unlikely to explain our findings though other, non-Mendelian genetic factors may play a role. Similar to results in non-Hispanic whites, a recent study confirmed the influence of polymorphisms in multiple genes on AD risk in Caribbean Hispanics but also suggested the presence of loci not known to be associated with AD(Lee et al., 2011). Such studies are yet to be done in the distinct population of Hispanics in the southwestern U.S. that is largely of Mexican and Central American origin.

There are several limitations to our study. The sample size is small, particularly with regard to those undergoing APOE genotyping, which was not performed randomly. Furthermore, since the population does not represent a purely community-based sample, we cannot generalize the rates of dementia, dementia subtypes or related demographic factors to the population at large. Also, we have not taken into account the heterogeneity of the non-Hispanic whites in the current study. This group represents a mix of persons of diverse

European and Middle Eastern ancestry and it is likely that there are differences dementia-related factors within this population that we could not address.

Another limitation of this study is the use of the MMSE as the indicator of dementia severity. The MMSE is known to have limitations in southern California Hispanics(Escobar et al., 1986). In order to minimize this effect, a culturally appropriate MMSE version was used and scores adjusted for age and education according to a formula employed for ethnic minority populations. However, it is impossible to completely eliminate biases from such a measure. Also, the staff evaluating the Hispanics and non-Hispanic whites were distinct, possibly introducing interviewer bias. However, the use of inter-rater training sessions and the presence of staff from both institutions at consensus conferences should serve to reduce such an influence.

It is possible that differences in recruitment methods between the Hispanic and white non-Hispanic population influenced our findings. Specifically, though community-based techniques were employed in both populations, it is likely that proportionally more Hispanics were recruited from the community and white non-Hispanics were referred from memory clinics. We unfortunately did not have adequate data regarding referral sources to analyze their influence on our findings. However, Hispanic subjects, despite their younger ages and recruitment from the community, tended to present in a more advanced stage of illness.

Also, the substantially lower levels of education in the Hispanic population may serve to lower the threshold at which dementia is detected in this population and therefore in part explain the earlier age of diagnosis. However, the fact that the age difference continued to be found when dementia severity was taken into account suggests that it is not the entire explanation.

Conclusions

Our results support previous observations that the age of dementia onset tends to be younger in Hispanics and extends this observation to Hispanics living in southern California who are more frequently of Mexican or Central American ancestry. Though education levels varied markedly between our Hispanic and white non-Hispanic cohorts, the effect was maintained when controlling for education, dementia severity, and history of hypercholesterolemia, hypertension, or diabetes. As the frequency of the APOE ε4 allele was lower in the Hispanic than the non-Hispanic group, our results indicate that other genetic or possibly reversible environmental risk factors may contribute to an earlier onset in Hispanics.

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Key Points

1. We found that the age of dementia diagnosis was significantly younger in a Hispanic population living in Southern California relative to a non-Hispanic population
2. This effect was maintained when controlling for years of education and was maintained at all levels of dementia as indexed by MMSE score, suggesting it was at least in part independent of education and disease severity.
3. History of hypertension, diabetes, or hypercholesterolemia similarly did not significantly influence the age of dementia onset.
4. This effect was present despite Hispanics having a similar prevalence of the APOE ε4 allele, suggesting other factors contribute to this difference.

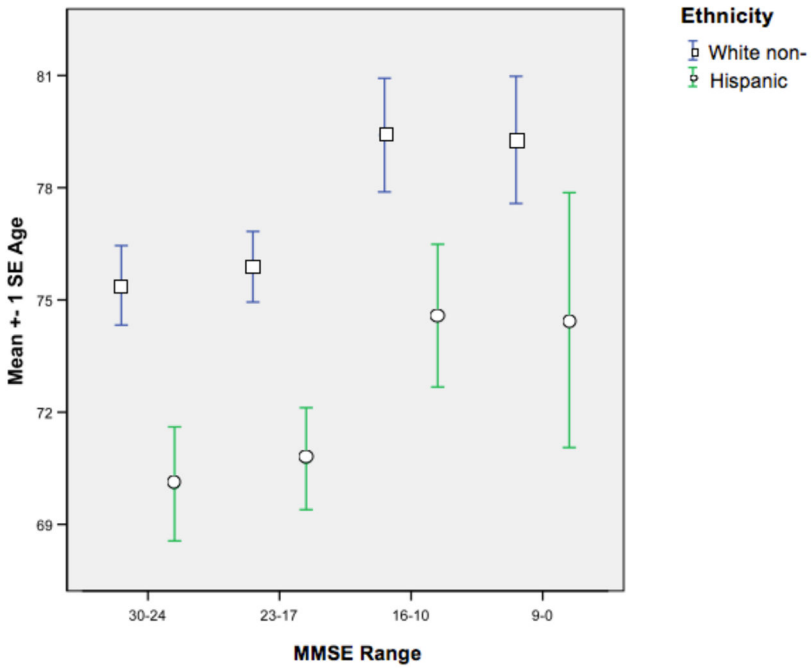

Figure 1.
Age at dementia diagnosis by ethnicity and dementia severity level

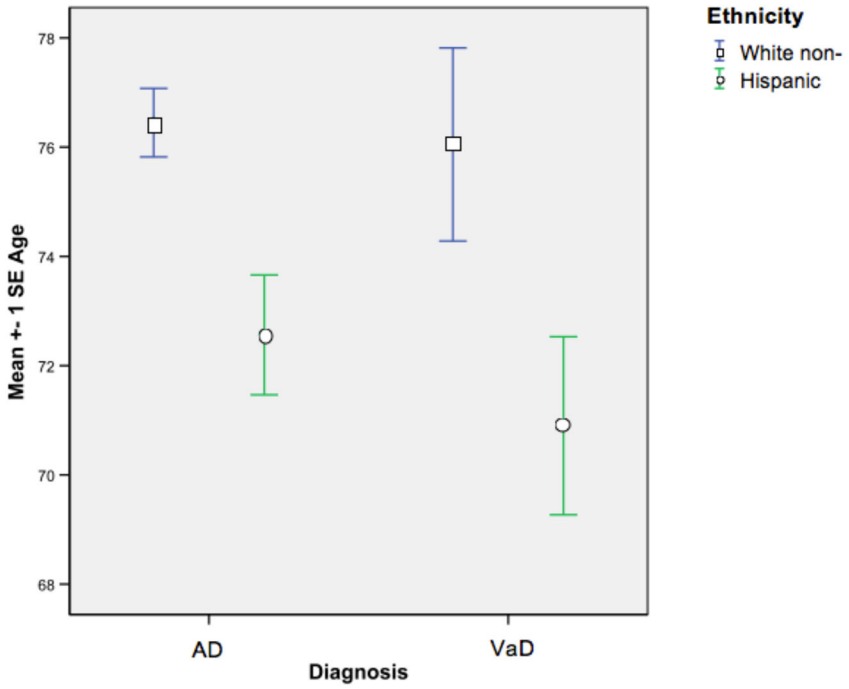

Figure 2.
Mean age at dementia diagnosis by ethnicity and type of dementia

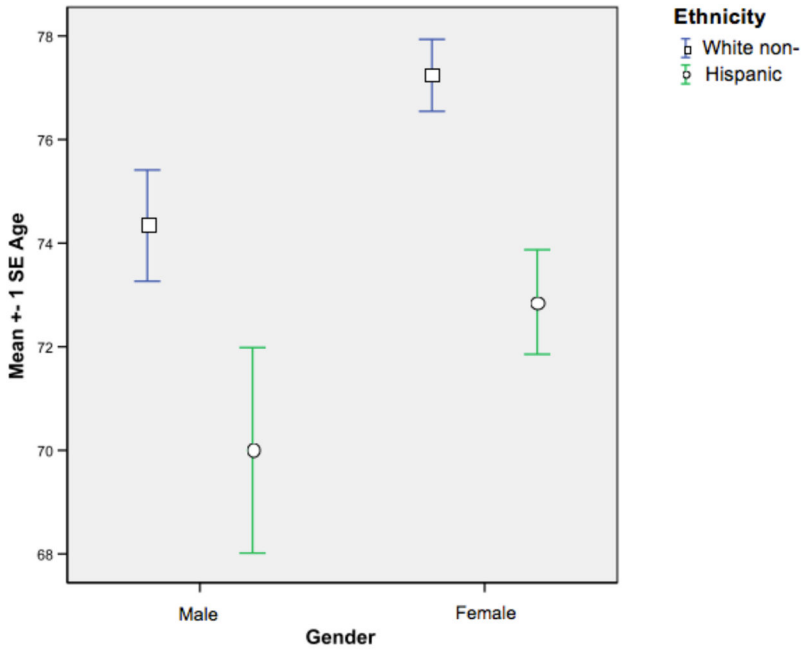

Figure 3.
Mean age at dementia diagnosis by ethnicity and gender

Table 1

Socio-demographic and clinical differences between ethnic groups. Significance levels represent results of t-tests, χ^2 tests, and (*) Kendall's tau-b test.

Measure	Hispanic(n = 110)	White, non-Hispanic(n = 180)	p value
Age at Diagnosis (mean ± s.e.)	72.1± 0.9	76.4± 0.6	p < 0.001
Gender (Male/Female)	29/81	52/128	N.S.
Education (mean yrs ± s.e.)	6.3± 0.4	12.6± 0.3	p < 0.001
MMSE Score (mean± s.e.)	15.2± 0.7	19.3± 0.5	p < 0.001
MMSE Adj Score (mean ± s.e.)	17.8± 0.7	19.7± 0.5	p = 0.01
MMSE scores			
24–30	17 (15.5%)	54 (30%)	p = 0.001*
17–23	28 (25.5%)	77 (43%)	
10–16	45 (41%)	27 (15%)	
≤9	20 (18%)	22 (12%)	
Diagnosis			
AD	80 (73%)	159 (88%)	p = 0.001
VAD	30 (27%)	21 (12%)	
APOE% with ε4 allele	12/43 (28%)	12/25 (48%)	N.S.
Hypertension	61 (59%)	88 (49%)	N.S.
Elevated cholesterol	36 (35%)	50 (28%)	N.S.
Type II Diabetes	29 (28%)	19 (11%)	p < 0.001

Table 2

Stepwise regression analysis of age at dementia diagnosis by socio-demographic and clinical variables

Variable	Beta	t	p value
MMSE	−.11	−1.35	0.18
Gender	2.58	2.19	0.03
Education	−.04	−.29	0.77
Diagnosis	−1.41	1.00	0.32
Diabetes	.73	.50	0.62
Hypertension	−1.46	−1.28	0.20
Cholesterol	.08	.06	0.95
Ethnicity	−4.65	−3.45	0.001