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RESEARCH ARTICLE

Functional measures and AD biomarkers among Hispanic and White non-Hispanic older adults

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Abstract

INTRODUCTION: Poorer baseline functioning is associated with long-term cognitive decline among Hispanic older adults, but little is known about associations of these factors with Alzheimer's disease (AD) neuroimaging biomarkers.

METHODS: A total of 461 Hispanic and White non-Hispanic (NHW) older adults who are cognitively normal ($n = 76$), had impaired cognition without mild cognitive impairment (MCI) ($n = 41$), or carried a diagnosis of MCI ($n = 253$) or dementia ($n = 91$) completed neuropsychological and functional assessment, genetic testing, and brain magnetic resonance imaging (MRI). Structural equation modeling (SEM) was used to examine predictive associations between functional and cognitive measures of AD neuroimaging biomarkers.

RESULTS: MRI volumes significantly predicted functional limitations in both groups. Sex and amyloid load significantly predicted functional limitations among the Hispanic group only. Years of education and MRI regional volume were the strongest predictors of cognition among both groups.

DISCUSSION: Results indicate that functional performance is associated with early AD biomarkers among Hispanic older adults. Clinical implications are discussed.

KEYWORDS
AD biomarkers, Alzheimer's disease, functional assessment, Hispanics, Latino/a/e/x

Highlights

- The current study addresses health disparities in Alzheimer's disease (AD) and related dementia assessment among Hispanics by identifying measures sensitive to early AD biomarkers.
- Associations of functional measures with AD genetic and neuroimaging biomarkers revealed that similarities in these associations exist between Hispanic and White

non-Hispanic individuals, but biological sex and amyloid load significantly predicted functional limitations among the Hispanic group only.

- These results have clinical implications for physicians who treat Hispanic AD patients and indicate that when compared to traditional diagnostic assessments, functional assessments may better aid in AD diagnostic precision among Hispanics.

1 | BACKGROUND

Compared to White non-Hispanics (NHWs), Hispanic Americans are 1.5 times more likely to have Alzheimer's disease (AD) and related dementia (ADRD) and more likely to have missed dementia diagnoses.[1–3] By 2060, the AD prevalence in elderly Hispanics is projected to increase sevenfold over current estimates.[3] Considering that Hispanics are the fastest growing ethnic group in the nation, it is imperative to study factors that contribute towards ethnic and racial disparities in ADRD diagnosis, such as clinical presentation, including symptom severity and performance on neuropsychological assessments,[4] genetic, and neuroimaging biomarkers.

AD is characterized by neurodegeneration that results in memory loss and cognitive deterioration accompanied by a decline in functional status. Biomarkers such as regional brain atrophy in medial temporal regions are strongly associated with robust discriminatory power for detecting overall cognitive impairment and predicting progression to AD.[5–7] These can distinguish cognitive stages (ie, cognitively normal [CN], mild cognitive impairment [MCI], and dementia) using structural magnetic resonance imaging (MRI) scans,[8,9,10] which are less influenced by confounding variables than other methods[11] and more accurately represent AD stages.[12]

Genetics plays a major role in at least 80% of AD cases. Gene polymorphisms, such as the $\varepsilon 4$ allele of the apolipoprotein E gene (*APOE*), influence susceptibility for late-onset ($\geq$ 60 years) AD in about 50% of cases.[13] Genotypically, *APOE* $\varepsilon 4$ appears to be less common among Hispanics when compared to NHWs and differs in its associations with AD neuropathology.[14–16] This demonstrates a paradox given the higher prevalence of AD diagnosis among Hispanics. Studying factors that uniquely contribute to AD neuropathology and diagnosis among Hispanics can shed light on this inconsistency and improve diagnosis and treatment.

The accumulation of amyloid-beta (Aβ) plaques in the brain is a known AD neuropathology and one of the earliest signs of the disease. Aβ plaques accumulate in the brain up to 20 to 30 years before AD diagnosis, increase with age, and can be found in normal functioning individuals who never develop AD. Much of what is known about the associations of Aβ and AD development is from studies that have historically included predominately NHW samples.[17–19] Previous studies examining Aβ among Hispanics have demonstrated mixed findings. Results of some studies suggest that Hispanics with a confirmed AD diagnosis have fewer Aβ plaques when compared to NHWs. Other studies, such as a study conducted by Santos and colleagues[20] found no difference in the presence of Aβ plaques among Hispanics versus NHWs. These inconsistencies in results may be explained by methodological limitations (eg, convenience samples, variability in the country of origin among research participants, and acculturation status as confounding variables).

Cognitive measures are often used to support ADRD diagnoses. Compared to NHW older adults, previous studies demonstrate that Hispanic ADRD patients perform worse on cognitive diagnostic measures even when controlling for mediating factors, and performance on these measures may not be reflective of AD neuropathology among Hispanics.[21–24] Hispanics are younger at AD onset and display higher cognitive deficits than NHWs.[25] Several confounding variables have been identified to mediate phenotypical differences, including educational attainment, age, gender, socioeconomic status, geographical regions, emotional functioning, monolingualism versus bilingualism, acculturation, and test efforts.[26–28] However, studies adjusting for these mediating factors have demonstrated that disparities in cognitive performance persist.[21]

Cognitive and functional decline in AD occurs due to the buildup of Aβ plaques. Functional status is determined by the ability to do basic activities of daily living (ADL) (eg, cooking, eating, showering, getting dressed, shopping, and housekeeping) and more complex instrumental ADL (IADL) (eg, community involvement, driving, healthcare management) necessary to maintain a level of independence. Functional evaluation is relevant for safety, care planning, diagnostic decisions, and recommendations. Detection of functional changes, using appropriate scales, may help identify those with MCI and those at a higher dementia risk. While subtle functional impairment may be present in MCI cases, the severity of functional impairment is associated with the probability of progression from MCI to dementia.[29] Among elderly Hispanics, there is evidence that suggests that poorer baseline clinical functioning is associated with long-term cognitive decline among Hispanics.[30] However, functional status can be subtle and difficult to ascertain.

The aim of the current study was to identify relationships among measures of clinical functioning, cognitive test performance, MRI volumes, and amyloid load, while adjusting for age, education, and *APOE* $\varepsilon 4$ status, and to test if the relationships were invariant among Hispanic and NHW participants. It was hypothesized that stronger associations among these measures would be identified among Hispanic individuals than in NHWs.

2 | METHODS

2.1 | Participants and recruitment

Participants were recruited from subjects enrolled in the 1Florida Alzheimer's Disease Research Center (1FL ADRC), Clinical Core in Miami Beach, FL, between 2015 and 2018. This study included 461 participants aged 65 and over who were CN (n = 76), had impaired cognition without MCI (n = 41), had MCI (n = 253), or had dementia (n = 91). Table 1 displays the demographic information of the participants. Participants were divided by ethnicity into those who were Hispanic (n = 258) and NHWs (n = 203). 1FL ADRC participants and their study partners/informants provided written informed consent to participate in an additional study where information was obtained on their clinical functioning in ADLs and IADLs. Information on cognitive functioning and AD biomarkers was previously collected by the 1FL ADRC at each participant's baseline visit. The Institutional Review Boards at Mount Sinai Medical Center, Miami Beach, FL, and Albizu University, Miami, FL, approved this study.

2.2 | Inclusion/exclusion criteria

Participants were included in the study if they (1) were 60 to 90 years old; (2) had a minimum sixth-grade education and reading level; (3) identified either English or Spanish as their primary language; (4) had a study partner; (5) had an age and education-corrected Montreal Cognitive Assessment (MoCA) score of 20+; and (7) were willing to complete the functional assessment. Participants were excluded if they had significant sensory (visual and hearing) or motor deficits, clinical stroke, or major medical or psychiatric illnesses that might prevent participation.

2.3 | Neuropsychological evaluation

Baseline neuropsychological data from 1FL ADRC participants were included in this study. Neuropsychological testing was administered in the participants' preferred language to self-identified Hispanic and non-Hispanic participants by a Spanish-English bilingual psychometrician who was blinded to the clinical evaluation. The neuropsychological battery included the following tests: (1) the Hopkins Verbal Learning Test Revised (HVLT-R)[31]; (2) the Weschler Memory Scale-Revised (WMS-R) Logical Memory subtest; (3) letter (F, A, and S) and category fluency[32]; (4) the Wechsler Adult Intelligence Scales Fourth Edition (WAIS-IV) Block Design subtest[33]; and (5) parts A and B of the Trail Making Test.[34] Translated and standardized Spanish versions of all tests were used with the corresponding age and education normative data.[35–38]

2.4 | Functional measure

Our team created a modified version of the Clinical Dementia Rating (CDR) Scale:[39] the mCDR.[40] The mCDR implements the use of a multiple-choice response format while excluding objective testing. This differs from the CDR which is an open-ended measure that requires a clinician to administer and score the results. The mCDR scale's multiple-choice response format facilitates focused answers, which also reduces administration time. It divides functional decline into the following categories: no functional decline, questionable functional decline, very mild but evident functional decline, mild and evident functional decline, and moderate functional decline, on a scale of 0 to 2. This is done by asking participants to compare previous and current performance as "no change (0)," "questionably worse (0.5)," "worse (1)," or "much worse (2)." The mCDR can be administered by a trained psychometrist or staff and minimizes the need for a trained clinician.

The mCDR demonstrated moderate-to-good inter-rater reliability in an ethnically diverse sample with a two-way random, single measure, absolute agreement intraclass correlation of 0.73, $F(40, 40) = 6.24$, $p < .001$. Multiple regression revealed that the language (English vs Spanish) of the mCDR form did not moderate the relationship between the two rater's scores ($\beta = 0.72$, $p < 0.001$). With respect to validity, the mCDR was correlated at –0.75 with the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for use in Mild Cognitive Impairment (ADCS-ADL-MCI; administered concurrently), indicating that there was a high degree of convergent validity between the two measures (56% shared variance). Further, the mCDR demonstrated 78% sensitivity and 90% specificity for an MCI diagnosis among NHWs,

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (eg, PubMed and MEDLINE). Health disparities exist among Hispanic older adults in the assessment and treatment of Alzheimer's disease (AD) and related dementias and there is a critical need to study factors that contribute towards these disparities. Hispanic older adults perform worse on cognitive tests when compared to White non-Hispanics and clinical functioning among this group is associated with long-term cognitive decline. Associations between functional and cognitive assessments of AD biomarkers are poorly understood.
2. **Interpretation**: Our findings indicated that sex and amyloid load significantly predict functional impairment among Hispanic older adults, indicating that the consideration of functional assessments may improve diagnostic precision among this group.
3. **Future directions**: Future studies should examine these associations among larger and ethnically diverse samples, as well as examine associations of AD blood-based and neuroimaging biomarkers to longitudinal clinical functioning among Hispanics.

TABLE 1 Demographic comparisons.

	Hispanic	Non-Hispanic White	Comparison
N	258	203	
Age	71.35 (7.99)	72.93 (8.13)	$t(430.37) = 2.08$ $p = 0.38$
Education	14.67 (3.78)	16.23 (3.18)	$t(445.01) = 4.76$ $p < 0.01$***
Gender			
Female	163	111	$\chi^2 = 3.40$ $p = 0.07$
Male	95	92	
No ε4 allele	149	100	$\chi^2 = 0.25$ $p = 0.88$
APOE ε4 status			
1 copy of ε4 allele	67	40	
2 copies of ε4 allele	12	8	
Normal cognition	38	38	$\chi^2 = 3.49$ $p = 0.32$
Cognitive status			
Impaired-not-MCI	19	22	
MCI	148	105	
Dementia	53	38	
CDR sum of boxes	2.42 (3.83)	2.44 (3.90)	$t(430.16) = 0.04$ $p = 1.00$
Estimated total intracranial volume (*T* score)	49.33 (9.72)	51.88 (9.85)	$t(322.88) = 2.42$ $p = 0.16$
MRI regional volume composite (*T* score)	50.63 (10.15)	49.30 (9.69)	$t(332.60) = 1.25$ $p = 1.00$
Amyloid PET SUVR Centiloid score	32.06 (37.35)	28.55 (41.08)	$t(247.51) = 0.73$ $p = 1.00$
Functional limitations composite (*T* score)	50.46 (10.60)	49.42 (9.17)	$t(454.81) = 1.13$ $p = 1.00$
Memory composite (*T* score)	48.79 (9.90)	51.54 (9.94)	$t(433.01) = 2.96$ $p = 0.03$*
Letter fluency composite (*T* score)	47.06 (8.38)	53.73 (10.65)	$t(376.60) = 7.31$ $p < 0.01$***
Category fluency composite (*T* score)	48.56 (8.70)	51.83 (11.20)	$t(373.14) = 3.42$ $p = 0.01$**
Trails B completion time (reflected *T* score)	51.79 (11.87)	47.73 (6.26)	$t(406.18) = 4.72$ $p < 0.01$***

Note: Bonferroni correction was used for multiple independent *t*-test comparisons.
Abbreviation: *APOE* ε4, apolipoprotein E gene ε4 allele; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standard uptake value ratio. *p<.05, **p<.01, ***p<.001.

61% sensitivity and 78% specificity among Hispanics, with perfect sensitivity and specificity for a dementia diagnosis among NHWs, and 95% sensitivity and perfect specificity among Hispanics. These findings suggest that the mCDR can aid accurate MCI diagnosis when administered to Hispanic older adults, whereas other commonly used measures such as the Functional Assessment Questionnaire (FAQ) lack data on MCI diagnosis among Hispanics.

2.5 | Diagnostic procedures

Cognitive diagnoses follow the NACC D1 classification protocol, which includes CN, amnestic and non-amnestic MCI, and dementia.

Diagnostic criteria for CN are (a) 60+ years of age; (b) no evidence of a memory complaint preferably confirmed by an informant; (c) MMSE score of 26+; (d) global CDR Scale of 0; (e) no neuropsychological

impairment; and (f) no functional impairment reflected on the CDR or FAQ scores.

For MCI, the diagnostic criteria are (a) 60+ years of age; (b) memory complaint(s), preferably confirmed by an informant; (c) a CDR scale score of 0.5; (d) MMSE score of 24+; (e) no impairment in social and/or occupational function; (f) no evidence of Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for Major Neurocognitive Disorder; and (g) confirmation of memory impairment at 1.5 SD or greater below expected levels, based on age- and education-adjusted normative data for each cultural/language group, on the HVLT-R delayed recall or on the delayed paragraph recall of the Wechsler Memory Scale, 3rd edition (WMS-III).

Diagnostic criteria for mild dementia are (a) 60+ years; (b) memory complaint preferably confirmed by an informant; (c) global CDR score of 1.0+ (total sum of box scores 4.5+); (d) MMSE score of 20+; (e) HVLT-R delayed recall or WMS-III delayed paragraph recall scores; and (f) though not required, non-amnestic impairment may be present at >1.5 SD below normative values in one or more domains (language, attention, visuospatial, and executive function).

2.6 | MRI imaging

MRI scans were performed using a Siemens Skyra 3T MRI scanner. MRI scans were evaluated by visual inspection as well as with T2 weighted FLAIR (5 mm thick sequential axial slices), and a 3D T1 weighted volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence (which provides high tissue contrast and high spatial resolution with whole brain coverage) to quantify brain atrophy.

Amyloid positron emission tomography (PET) scans were performed using the tracer (18-F) Florbetaben and procedures described in 2019 by Duara et al.[41] Quantitative assessment of PET scans was obtained using a composite standard uptake value ratio (SUVR) calculated by the ratio of the mean SUVR of the six cortical regions (frontal, temporal, parietal, precuneus, anterior and posterior cingulate cortex regions, with each region summed from left and right hemispheres) to the cerebellar gray matter. We used the formula for derivation of Centiloid values from SUVR, using the tracer Florbetaben, as described by Rowe et al.[42] For the qualitative/visual assessment of PET scans, all Aβ PET scans were read initially by an independent, trained radiologist, who was not otherwise involved in this study, and a trained and experienced reader (RD), both of whom were blinded to the cognitive and clinical diagnosis, using a methodology similar to that described.[43,44] Images are displayed using a reader adjustable gray scale calibrated by providing optimal discrimination of the cerebellar gray matter from white matter.[45] A final dichotomous (A+ versus A−) diagnosis is made by each reader. Interrater reliability was assessed on 95 PET scans, in which the agreement between the two readers has been evaluated and found to be 93.2% for positive scans and 100% for negative scans.

2.7 | *APOE* genotyping and polygenic risk scores procedures

All samples were genotyped in a laboratory for *APOE* ε2, ε3, and ε4 alleles using predesigned TaqMan SNP genotyping assays for SNPs rs7412 and rs429358 (Thermo Fisher Scientific, Massachusetts, USA) on the Quant Studio 7 Flex Real-Time PCR system (Applied Biosystems, California, USA) following the manufacturer's protocol.

2.8 | Data analysis

T-tests and chi-square analyses were conducted for comparison of demographic variables (Table 1). To examine predictive associations of functional and cognitive measures with AD neuroimaging biomarkers, structural equation modeling (SEM) was used. This is a multivariate analysis that is a combination of factor and multiple regression analysis and analyzes structural relationships between measured variables and latent constructs. Further, invariance testing procedures were used during which SEM models are estimated separately for Hispanic and NHW groups, but an increasing amount of model constraints are added in a stepwise manner, forcing the separate models to be increasingly alike (or "invariant"). Model fit is examined after each step to determine if the imposition of these equivalency constraints on the separate models worsens their model fit. We chose this method because of it is best equipped to show how multiple constructs are related to other individual constructs and test to what extent these relationships can be said to be invariant across different groups of people. All statistical analyses were performed using *R*.

3 | RESULTS

Table 1 illustrates comparative results for all variables included in the study. The Hispanic group had significantly lower levels of education when compared to the NHW group and significant differences existed regarding performance on cognitive measures, with the Hispanic group demonstrating poorer performance. No significant differences between groups were evident for *APOE* ε4 status, MRI regional volume, amyloid PET, or mCDR scores (functional composite). The ethnic groups did not significantly differ in cognitive status/diagnosis or in CDR sum of boxes total score.

Using the baseline data for participants of the 1FL ADRC, the SEM model depicted in Figure 1 was fit separately for NHW (N = 203) and Hispanic participants (N = 258). Age, gender, years of education, total intracranial volume, number of ε4 alleles, MRI regional volume composite, and PET Centiloid scores were all included as predictor variables in the model. The functional limitations composite included scores from each domain of the mCDR. The memory composite consisted of the delayed recall scores from the HVLT-R and WMS-R logical memory tests. Letter and category fluency composites were created from total number of words for each individual letter or category. Finally,

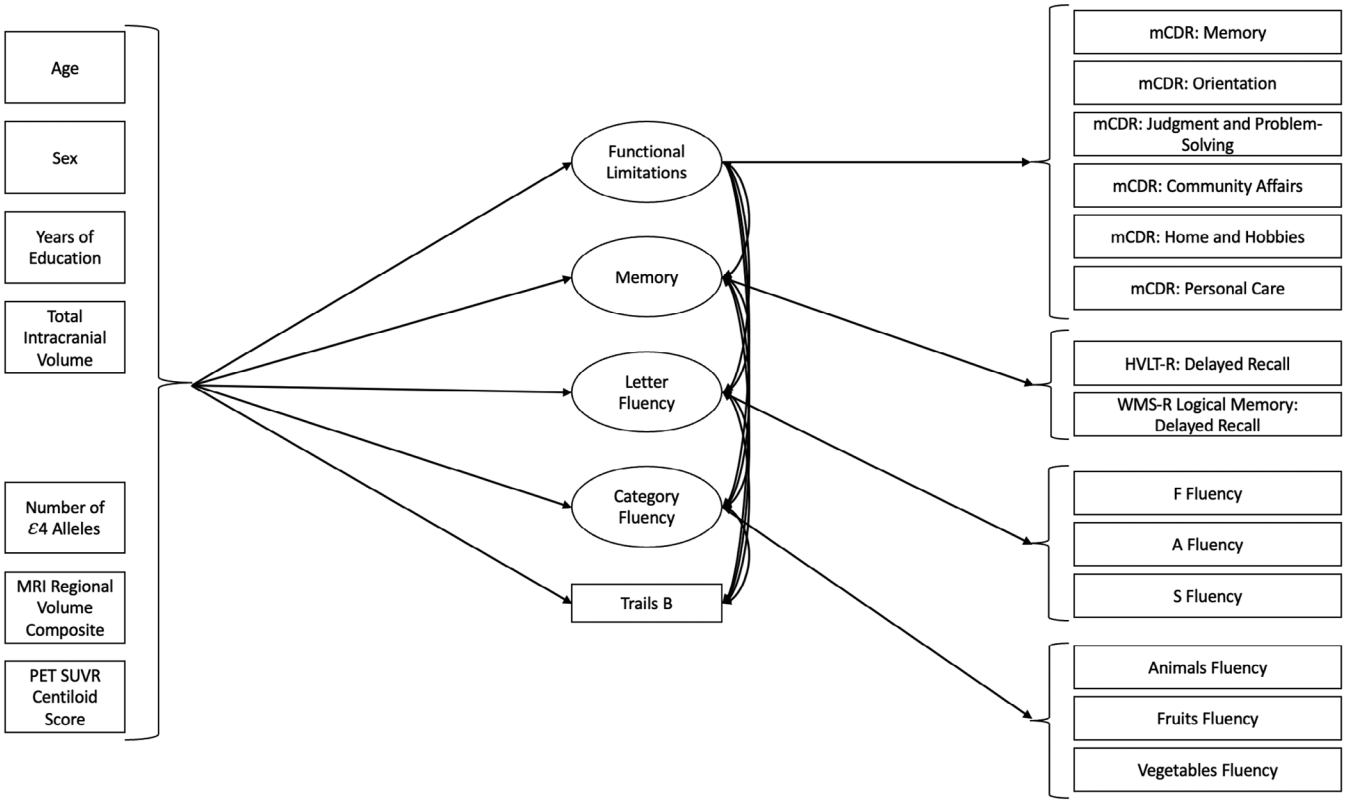

FIGURE 1 Structural equation model. HVLT-R, Hopkins Verbal Learning Test Revised; mCDR, modified Clinical Dementia Rating; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standard uptake value ratio; WMS-R, Wechsler Memory Scale -Revised.

we included Trails B as our measure of executive functioning in the SEM model. Full information robust maximum likelihood estimation was used. Imposing strict structural invariance (equal indicator loadings, intercepts, and uniqueness) did not significantly worsen model fit, $\chi^2(34) = 31.19$, $p > 0.05$. The structurally invariant model had good fit: $\chi^2(336) = 562.74$, standardized root mean square residual (SRMR) = 0.06, adjusted goodness of fit index (AGFI) = 0.91, comparative fit index (CFI) = 0.96, Tucker–Lewis index (TLI) = 0.95, root mean square error of approximation (RMSEA) = 0.05. See Table 2 for R^2 values for endogenous variables and Table 3 for factor loadings.

Imposing invariance in latent means did not significantly worsen model fit, $\chi^2(5) = 3.42$, $p > 0.05$; however, model fit was worsened by imposing invariance in latent variances, $\chi^2(5) = 76.45$, $p < 0.001$, covariances, $\chi^2(10) = 39.43$, $p < 0.001$, and regressions, $\chi^2(5) = 66.49$, $p < 0.001$.

Table 4 lists the results of the stratified regressions. MRI volumes significantly predicted functional limitations among both Hispanic ($\beta = -0.51$, $p < 0.001$) and NHW participants ($\beta = -0.42$, $p < 0.001$). Additionally, among Hispanic participants only, sex ($\beta = -0.17$, $p < 0.05$) and amyloid load ($\beta = 0.25$, $p < 0.001$) significantly predicted functional limitations. Similar associations were found between the two groups for predicting scores on memory, letter fluency, category fluency, and Trails B, with years of education and MRI regional volume being the strongest predictors. Among the Hispanic group only, the number of ε4 alleles significantly predicted performance on memory ($\beta = -0.18$, $p < 0.01$), sex predicted performance on letter fluency ($\beta = 0.22$, $p < 0.05$), and total intracranial volume ($\beta = -0.2$, $p < 0.05$) and PET SUVR ($\beta = -0.24$, $p < 0.05$) predicted category fluency scores.

Table 5 shows the stratified latent correlations and demonstrates that all the outcome measures were significantly correlated.

Overall, our results suggest that (1) the indicators are equivalently valid reflections of the latent constructs in each group, (2) the means of the latent constructs were equivalent between groups, (3) the two groups did not have homogenous variances in the latent constructs, and (4) the strengths of the relationships among the constructs and the exogenous predictor variables were different between the groups. In other words, the ethnic/racial grouping moderated the relationships among the endogenous constructs and exogenous predictors (as shown in Tables 4 and 5).

4 | DISCUSSION

The current study aimed to examine associations of a measure of clinical functioning with AD genetic and neuroimaging biomarkers among Hispanic and NHW older adults. We used SEM to measure predictive and possible causal relationships between our composite variables of functional limitations, memory, letter fluency, and executive function performance. Our findings indicate that although there are similarities in significant associations between both Hispanic and NHW groups

TABLE 2 Stratified R^2 values in structurally invariant (strict) model.

	R^2	
Measure	NHW	Hispanic
mCDR: memory	0.75	0.78
mCDR: orientation	0.87	0.89
mCDR: judgment and problem-solving	0.87	0.89
mCDR: community affairs	0.58	0.62
mCDR: home and hobbies	0.85	0.87
mCDR: personal care	0.42	0.46
WMS-R logical memory: Delayed recall	0.68	0.67
HVLT-R: delayed recall	0.50	0.49
F fluency	0.77	0.68
A fluency	0.71	0.60
S fluency	0.81	0.73
Animals fluency	0.68	0.56
Fruits fluency	0.78	0.69
Vegetables fluency	0.72	0.61
Functional limitations	0.23	0.39
Memory	0.37	0.61
Letter fluency	0.21	0.27
Category fluency	0.35	0.45
Trails B time	0.38	0.26

Abbreviations: HVLT-R, Hopkins Verbal Learning Test-Revised; mCDR, modified Clinical Dementia Rating; NHW, White non-Hispanic; WMS-R, Weschler Memory Scale-Revised.

TABLE 3 Stratified factor loadings in structurally invariant (strict) model.

		Standardized loadings	
Factor	Indicator	NHW	Hispanic
Functional limitations	mCDR: memory	0.87	0.88
	mCDR: orientation	0.93	0.94
	mCDR: judgment and problem-solving	0.93	0.94
	mCDR: community affairs	0.76	0.79
	mCDR: home and hobbies	0.92	0.93
	mCDR: personal care	0.65	0.68
Memory	WMS-R logical memory: delayed recall	0.83	0.82
	HVLT-R: delayed recall	0.71	0.70
Letter fluency	F fluency	0.88	0.83
	A fluency	0.84	0.78
	S fluency	0.90	0.86
Category fluency	Animals fluency	0.82	0.75
	Fruits fluency	0.88	0.83
	Vegetables fluency	0.85	0.78

Note: All loadings are significant at $p < .001$.
Abbreviations: HVLT-R, Hopkins Verbal Learning Test-Revised; mCDR, modified Clinical Dementia Rating; NHW, White non-Hispanic; WMS-R, Weschler Memory Scale-Revised.

across variables, functional limitations were related to sex and amyloid load among the Hispanic group only. This indicates that functional performance, as measured with the mCDR, is associated with AD imaging biomarkers, which are measures of the severity of underlying neuropathology.[46] We additionally found that associations between predictor variables and cognitive performance differed between the Hispanic and NHW groups.

While the association of both functional and cognitive measures with neuroimaging variables is well known,[47] to our knowledge, our study was among the first to examine associations between clinical functioning and multiple AD biomarkers among a Hispanic sample, and the first to investigate associations with amyloid PET. Previous research examined associations between performance on the FAQ and MRI structural volume across an ethnically diverse sample that included Hispanic Americans. Their findings indicated that FAQ scores significantly predicted hippocampal volume, and ethnicity had a moderating effect, with better functioning predicting higher hippocampal volumes among younger Hispanic females.[48] Our findings were consistent with the results of this study in that both our Hispanic and NHW groups demonstrated significant associations between clinical functioning and MRI composite variables, and sex significantly predicted clinical functioning among the Hispanic group only. Our findings add to these previously identified associations by determining that amyloid load significantly predicts performance on the mCDR measure among Hispanics but not NHWs. These findings not only highlight associations between our measure and ADRD biomarkers in the assessment of Hispanics, but also provide a further understanding of factors that uniquely affect the aging process and indicate that sex as a biological variable and amyloid load are significant predictors of clinical functioning among Hispanics.

Comparative analyses revealed that although our participants carried similar diagnoses, they significantly differed in performance on cognitive measures, with Hispanics performing worse than NHWs. This is consistent with previous findings confirming that these differences exist[49] and further highlights the importance of identifying alternative measures that can better aid in the AD diagnostic precision required in clinical practice. It should be noted that in fact, there were no significant differences between the two ethnic groups on diagnostic scores or CDR sum of boxes (our gold standard of clinical functioning), which indicates that the observed differences in our results can more confidently be attributed to the ethnicity factor rather than disease stage. Other studies that examined associations among

TABLE 4 Stratified regression standardized betas in structurally invariant (strict) model.

		Standardized betas	
Factor	Predictor	NHW	Hispanic
Functional limitations	Age	0.00	−0.07
	Sex (reference = male)	−0.13	−0.17*
	Years of education	−0.16	−0.02
	Total intracranial volume	0.11	0.15
	Number of ε4 alleles	−0.01	0.09
	MRI regional volume composite	−0.42***	−0.51***
	PET SUVR Centiloid score	0.08	0.25***
Memory	Age	−0.11	0.08
	Sex (reference = male)	0.19	0.10
	Years of education	0.25***	0.19**
	Total intracranial volume	−0.12	−0.16
	Number of ε4 alleles	−0.15	−0.18**
	MRI regional volume composite	0.35***	0.42***
	PET SUVR Centiloid score	−0.23*	−0.46***
Letter fluency	Age	0.12	0.00
	Sex (reference = male)	0.16	0.22*
	Years of education	0.29***	0.29***
	Total intracranial volume	−0.05	0.01
	Number of ε4 alleles	0.13	−0.01
	MRI regional volume composite	0.33***	0.35***
	PET SUVR Centiloid score	−0.13	−0.07
Category fluency	Age	−0.07	0.05
	Sex (reference = male)	0.31***	0.23**
	Years of education	0.24***	0.22**
	Total intracranial volume	−0.08	−0.2*
	Number of ε4 alleles	0.06	−0.07
	MRI regional volume composite	0.37***	0.48***
	PET SUVR Centiloid score	−0.16	−0.24**
Trails B time	Age	−0.02	0.02
	Sex (reference = male)	0.04	0.09
	Years of education	0.27***	0.29***
	Total intracranial volume	−0.27**	−0.17
	Number of ε4 alleles	−0.05	−0.1
	MRI regional volume composite	0.45***	0.28**
	PET SUVR Centiloid score	−0.21*	−0.18**

Note: Trails B time scores were reflected such that higher scores indicate better performance.

Abbreviations: MRI, magnetic resonance imaging; NHW, White non-Hispanic; PET, positron emission tomography; SUVR, standard uptake value ratio.

*$p < .05$; **$p < .01$; ***$p < .001$.

TABLE 5 Stratified latent correlations in structurally invariant (strict) model.

		Correlation	
Factor	Factor	NHW	Hispanic
Memory	Trails B time	0.39***	0.27**
Memory	Letter fluency	0.36***	0.32**
Memory	Word fluency	0.75***	0.64***
Memory	Function limitations	−0.53***	−0.48***
Trails B time	Letter fluency	0.46***	0.32***
Trails B time	Word fluency	0.47***	0.33**
Trails B time	Function limitations	−0.54***	−0.24*
Letter fluency	Word fluency	0.54***	0.56***
Letter fluency	Function limitations	−0.38***	−0.17
Word fluency	Function limitations	−0.46***	−0.39***

Abbreviations: NHW, White non-Hispanic.

*$p < .05$; **$p < .01$; ***$p < .001$.

Hispanic groups of clinical functioning with cognition have found that informant-based ratings of functional impairment are not only significantly associated with cognitive performance, but can identify patients who are at increased risk for future cognitive decline.[30] Studies examining associations between the presence of *APOE* ε4 and ADRD have demonstrated that these relationships differ among Hispanics, and vary by continental ancestry.[50] For example Gonzalez et al.[51] identify the ε4 allele as being more common among Caribbean Hispanics when compared to Central Americans. O'Bryant and colleagues[44] found that the frequency of ε4 and ε2 alleles is lower among Mexican Americans than among NHWs, and *APOE* ε4 frequency was associated with immediate and delayed memory, while among NHWs it was associated with memory as well as executive functioning and verbal fluency. Our results indicated no differences in the frequency of *APOE* ε4 between ethnic groups, which could be attributed to diagnostic variability and our sample predominately being of Caribbean countries of origin. We also found that the number of ε4 alleles was associated with performance on immediate and delayed memory measures among the Hispanic, but not the NHW group. These findings are relevant for understanding these associations among Hispanic older adults with varying levels of cognitive performance. In our study, we found no unique associations (ie, the relationship after controlling for all the other variables in the model, eg, amyloid load as measured by PET SUVR) between the number of ε4 alleles and any of the other neuropsychological factors nor our measure of clinical functioning among our Hispanic sample.

Limitations of our study include the generalizability of our sample. We conducted this study in South Florida, where the distribution of the country of origin differs from that of the U.S. population. The demographic of Hispanics in the U.S. is diverse and includes 61.6% Mexican, 9.6% Puerto Ricans, 9.3% Central Americans, 6.4% South Americans, and 13.1% from other Hispanic countries46. Comparatively, in Florida, 41% of Hispanic residents are Cuban, 18% are Puerto Rican, 17% are Mexicans, and 13% are South Americans.[49] Future research should replicate our study across regions and include a Hispanic sample with

diverse countries of origin. Doing so would provide results that are generalizable to the U.S. Hispanic population. Other limitations include the sample size. This study could be replicated in a larger, ethnically diverse sample to increase statistical power and significance.

The focus of our study was to introduce the mCDR as a new tool that has been validated in Spanish speakers, and which has demonstrated good sensitivity and specificity for detecting an MCI diagnosis. We recognize that other commonly used tools such as the FAQ are adequate tools to measure clinical functioning, but the FAQ has been shown to be sensitive to education and there is no sensitivity or specificity for MCI diagnosis for Hispanic/Spanish speakers. Future work should examine associations of other measures of clinical functioning to AD biomarkers. Future research should also examine whether observed ethnic differences persist across disease stages among a larger sample with enough statistical power to address this question.

In summary, our study sought to address existing disparities in ADRD diagnosis by examining associations of an informant-based functional measure with AD biomarkers among Hispanics and NHWs and found that AD biomarkers are similarly predictive of cognitive functioning between the two groups. Still, amyloid load, one of the earliest signs of AD, is a better indicator of impaired functional performance among Hispanics than in NHWs. Our findings demonstrate that informant-based functional measures can enhance diagnostic accuracy among Hispanics.

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CONFLICT OF INTEREST STATEMENT

Authors have no conflicts of interest to declare. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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