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Research Article

Impact of white matter hyperintensity volume on cognition among US Mexican American adults

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Abstract

Objective: Higher white matter hyperintensity (WMH) volume is a marker of cardiovascular disease (CVD) risk. CVD risk factors increase risk for Alzheimer's disease and related dementias (ADRD). Mexican Americans (MA) and individuals of other Hispanic/Latino heritages have higher risk for CVD and ADRD. However, knowledge of associations between WMH volume and cognition in these groups remains limited. **Method:** We conducted a cross-sectional study of associations between WMH volume and neuropsychological performance (attention/executive functioning, memory) in MA ($n = 851$) and non-Hispanic White (NHW; $n = 747$) adults in the Health and Aging Brain Study: Health Disparities. **Results:** The MA group (mean age = 63.72 ± 7.90 years; 66.3% female) had higher rates of consensus diagnoses of hypertension and diabetes, whereas the NHW group (mean age = 69.18 ± 8.65 years; 55.2% female) had higher rates of diagnosed CVD ($ps < .01$). WMH volumes were higher among individuals with CVD risk factors/conditions ($ps < .01$). There were differential associations between WMH and neuropsychological performance across ethnoracial groups ($ps < .001$), wherein associations were steeper in the NHW group than in the MA group. Lower educational level was associated with higher WMH volume in the NHW group ($p < .001$), but no association was seen in the MA group ($p > .05$). **Conclusions:** Negative effects of pathological changes in the form of WMH on cognition may be less robust or consistent for MA adults than NHW adults. Furthermore, the impact of WMH on cognition in NHW adults may be mitigated by cognitive reserve related to educational attainment.

Keywords: Aging; Alzheimer's disease; cardiovascular diseases; cognition; cognitive reserve; Hispanic or Latino

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Alzheimer's disease and related dementias (ADRD) affect about 13% of Hispanic/Latino (hereafter, Latino) adults ages 65 and older in the USA (Alzheimer's Association, 2020). Moreover, relative to older non-Hispanic White (NHW) adults, older Latino adults are about 1.5 times as likely to develop ADRD (Alzheimer's Association, 2020; Haan et al., 2003; Samper-Ternent et al., 2012). Furthermore, while ADRD prevalence is expected to increase among all ethnoracial groups through 2060, reflecting the growth of the aging population at large, the Latino population is projected to have the largest increase over that time frame (Matthews et al., 2019). Consisting of 62.5 million people and about 19% of the total population (U.S. Department of Health and Human Services, 2023), the Latino community in the USA is projected to further grow to over 100 million by the year 2060 (Matthews et al., 2019). Notably, 38.5 million or 62% of Latino individuals identify as Mexican American (MA) and are expected to remain the largest Latino subgroup in the USA. Further investigation of factors that increase risk for ADRD-related pathological changes in aging MA and other Latino adults will be imperative given current estimates and projections in the general growth of, as well as ADRD prevalence in this population.

Cardiovascular disease (CVD) is the leading cause of death for people of most ethnoracial groups in the USA (Centers for Disease Control and Prevention, 2018; Heron, 2017). The extant literature points to a robust association between CVD and cognitive impairment, and a history of CVD risk factors (e.g., hypertension, diabetes) can result in cognitive impairment that exceeds normal age-related changes (Kulshreshtha et al., 2019). CVDs and their risk factors also place individuals at increased risk for incident mild cognitive impairment (MCI) or dementia due to ADRD (Ganguli et al., 2013; Leritz et al., 2011; Stampfer, 2006).

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Among other factors, the high prevalence of CVD among MA individuals is likely to strongly contribute to ADRD health disparities. Several CVD risk factors have been shown to increase the risk of small vessel microvascular disease on magnetic resonance imaging (MRI) of the brain in the form of white matter hyperintensities (WMH), lacunar infarcts, and microbleeds (Kerola et al., 2011; Knopman & Roberst, 2010). WMH is a particularly common incidental finding linked to increased risk of dementia among individuals with CVD risk (Benjamin et al., 2016; Hu et al., 2021). Furthermore, higher WMH volumes have been shown to correspond with worse neuropsychological performance in ethnoracially diverse samples, particularly in the cognitive domains of executive functioning and processing speed (Brickman et al., 2011; Debette & Markus, 2010; Dong et al., 2010; Stavitsky et al., 2010). These findings are thought to reflect damage to the subcortical–frontal connections implicated in these cognitive domains (Biesbroek et al., 2017).

Community-based research studies have revealed ethnoracial differences in underlying risk factors, pathological changes, and clinical manifestations of ADRD (Babulal et al., 2019; González et al., 2019; O'Bryant et al., 2021). A limited body of research suggests that patterns of WMH and neuropsychological performance may differ across ethnoracial (e.g., Latino, non-Hispanic Black, NHW) groups. For example, Latino adults have been shown to have higher WMH volumes compared to NHW adults, accompanied by worse performance on neuropsychological tests (Rizvi et al., 2018; Zahodne et al., 2015). Moreover, Vintimilla et al. (2021) recently demonstrated with a cognitively unimpaired MA sample that WMH volume is associated with worse neuropsychological performance, particularly within the cognitive domain of executive functioning. However, whether the *strength* of associations between WMH volume and neuropsychological performance differs for Latino individuals versus those from other ethnoracial backgrounds remains unclear.

Latino adults show an earlier age of AD onset and are more likely to experience considerable delays in both diagnosis and treatment (Chin et al., 2011; O'Bryant et al., 2013). Factors including (but not limited to) lower educational levels may be contributors to the differences in ADRD presentation between Latino and NHW adults (Vega et al., 2017). Given early detection and prevention efforts are critical for reducing the burdensome high healthcare costs associated with ADRD, there is an urgent need to identify key factors underlying ADRD disparities among aging Latino adults, particularly among MAs. Furthermore, while efforts to increase recruitment and representation of Latino adults in cognitive aging research are expanding, MA adults remain underrepresented in and underserved by this research (Arevalo et al., 2016).

The aim of the present study was to examine potential interactive effects of ethnoracial background and WMH on neuropsychological outcomes in MA and NHW adults enrolled in the Health and Aging Brain Study: Health Disparities (HABS-HD). We hypothesized there would be differential (i.e., differences in magnitudes of the strength of) associations between WMH and neuropsychological performance, particularly in executive functioning, across MA and NHW participants. Study findings have the potential to bolster our current knowledge of associations of WMH with cognitive health in the underrepresented and underserved MA population, which has disproportionately high CVD and ADRD risk.

Method

Study design

The University of North Texas Health Science Center (UNTHSC) Institute for Translational Research initiated the HABS-HD project in 2017 to better understand the biological, social, and environmental factors that impact brain aging among diverse communities. The present study used publicly available data collected through November 2021 from the initial MA and NHW data collection wave. More information about the community-based participatory research approach of the HABS-HD study and the corresponding publicly available dataset can be found elsewhere (O'Bryant et al., 2021).

HABS-HD participants undergo a clinical interview, functional and neuropsychological assessments, blood draw for clinical and biomarker analysis, and brain MRI scan. All study procedures are completed during a baseline visit and, subsequently, every 24 months. While HABS-HD is a longitudinal project, the present study focuses on cross-sectional data from baseline visits. All participants provided written informed consent, and the procedures were all approved by the local Institutional Review Boards of the University of North Texas Health Science Center (site of data collection and processing) and the University of North Carolina at Chapel Hill and California State University San Marcos (sites of data analysis and manuscript writing). The present study conforms with the Declaration of Helsinki.

Participants

The present study included 1598 participants who (1) self-reported as MA (n=851; mean age = 63.72±7.90 years; 66.3% female) or NHW (n=747; mean age = 69.18±8.65 years; 55.2% female) (Table 1); (2) were 50 years of age or older; (3) reported Spanish or English as their primary language; (4) completed an interview and neuropsychological testing in Spanish or English; and (5) had data on all MRI variables of interest (i.e., WMH volume and intracranial volume [ICV]). Additional inclusion criteria based on general HABS-HD procedures include (1) willingness to provide blood samples and (2) ability to undergo neuroimaging studies. Exclusion criteria include (1) type 1 diabetes; (2) presence of active infection; (3) current/recent (within the past 12 months) cancer (other than skin cancer); (4) current severe mental illness that could impact cognition (except depression); (5) recent (within the past 12 months) traumatic brain injury with loss of consciousness; (6) current/recent substance (including alcohol) abuse; (7) active severe medical condition that could impact cognition (e.g., end-stage renal disease, chronic heart failure, chronic obstructive pulmonary disease); and (8) current diagnosis of dementia other than AD.

Participants were also classified on cognitive status (normal cognition, MCI, dementia) using HABS-HD consensus diagnosis procedures (O'Bryant et al., 2021). Consensus diagnoses of cognitive status were assigned based on self- and informant report of daily functioning, expert clinician assignment of Clinical Dementia Rating (CDR) scores (using cognitive and daily functioning data), and neuropsychological test results.

MRI acquisition

Imaging data were acquired using a 3T Siemens SKYRA scanner. Structural MRI scans were based on a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences,

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Table 1. Descriptive (means and standard deviations or percentages) and inferential statistics associated with demographic and clinical characteristics of the study sample

Demographic or clinical variable	MA $n = 851$	NHW $n = 747$	t or χ^2	p	d or V
Age (years)	63.72 ± 7.90	69.18 ± 8.65	$t(1596) = 13.18$	<.001	0.661
Sex (% female)	66.3	55.2	χ^2 (1598) = 20.70	<.001	0.114
Education (years)	9.45 ± 4.58	15.50 ± 2.60	$t(1596) = 31.88$	<.001	1.599
Primary language (%)			χ^2 (1598) = 825.93	<.001	0.719
Spanish	69.6	0			
English	30.3	99.9			
Other	0.1	0.1			
Interview language (%)			χ^2 (1598) = 748.47	<.001	0.684
Spanish	65.3	0			
English	34.7	100			
CVD risk factors/conditions (%)					
Hypertension	65.7	58.0	χ^2 (1598) = 9.74	.002	0.078
CVD	5.2	9.4	χ^2 (1598) = 10.59	.001	0.081
Diabetes	35.3	12.7	χ^2 (1598) = 108.56	<.001	0.261
Cognitive status			χ^2 (1598) = 16.46	<.001	0.101
Normal cognition	74.7	83.0			
MCI	17.9	11.5			
Dementia	7.4	5.5			

Note: MA = Mexican American, NHW = non-Hispanic White, CVD = cardiovascular disease, MCI = mild cognitive impairment. *t*-test statistics (*t*, *d*) are reported for continuous variables; chi-square test statistics (χ^2, *V*) are reported for categorical variables.

with the following acquisition parameters: repetition time (TR) = 2300 ms, echo time (TE) = 2.93 ms, matrix = 256, field of view = 270, 1.2 mm slice thickness, voxel size = 1.1 mm ×1.1 mm × 1.2 mm. The volume of WMH was extracted (see below) from a T2-weighted fluid attenuated inversion recovery (FLAIR) sequence, acquired with the following parameters: repetition time (TR)= 4.800 ms, echo time (TE) = 441 ms, TI time = 1650 ms, matrix = 256, field of view = 256, slice thickness = 1.2 mm, voxel size = 1.0 mm × 1.0 mm × 1.2 mm. Other MRI modalities acquired in the study are described elsewhere (Vintimilla et al., 2021). Our data release did not include information on the scanner used with each participant, and we were therefore unable to control for this variable. MRI variables of interest in the present study were WMH volume and ICV. WMH volumes were quantified by the HABS-HD imaging team using the lesion growth algorithm which is part of the Lesion Segmentation Toolbox in the Statistical Parametric Mapping (SPM) software (Vintimilla et al., 2021; King et al., 2022). A log transformation of WMH volume data was conducted given evidence of nonnormality during preliminary data checks. Estimates of ICV were derived from subjects' MPRAGEs by the HABS-HD imaging team using FreeSurfer 6.0.

Neuropsychological outcome variables

Neuropsychological outcomes examined in the present study were derived from measures available in the HABS-HD neuropsychological test battery that encompassed cognitive domains of executive functioning (Trail Making Test [TMT] Part B), processing speed (TMT Part A, Digit Symbol Substitution), attention (Wechsler Memory Scale-III [WMS-III] Digit Span Total), and memory (Spanish-English Verbal Learning Test [SEVLT] Learning, SEVLT Recall, WMS-III Logical Memory Immediate Recall, WMS-III Logical Memory Delayed Recall). The HABS-HD dataset provides neuropsychological *z*-scores that account for education, primary language, and age (O'Bryant et al., 2021). Composite *z*-scores in domains of (1) executive functioning, processing speed, and attention (hereafter, attention/EF) and (2) memory were generated by averaging *z*-scores across individual tests comprising each domain (i.e., one's composite *z*-score for attention/EF would be calculated as the average *z*-score across TMT Part A, TMT Part B, Digit Symbol Substitution, and WMS-III Digit Span Total; similarly, their composite *z*-score for memory would be calculated as the average *z*-score across SEVLT Learning, SEVLT Recall, WMS-III Logical Memory Immediate Recall, and WMS-III Logical Memory Delayed Recall). Given more consistent findings in the literature reflecting an impact of WMH on attention/EF, likely given the implication of subcortical–frontal networks in this domain (Brickman et al., 2011; Debette & Markus, 2010; Dong et al., 2010; Stavitsky et al., 2010), and that memory is conceptualized to involve a substantially different set of cortical networks (Salmon & Bondi, 2009; Salmon & Filoteo, 2007), memory was examined as a control/comparison domain in the present study.

CVD risk factors

Multiple CVD risk factors were captured when participants self-reported the following conditions: hypertension (yes, no), CVD (e.g., heart attack, heart failure, cardiomyopathy, atrial fibrillation, and/or heart valve replacement; yes, no), and diabetes (yes, no). Past medical history was corroborated by review of fasting clinical labs, vital signs, and current medications by healthcare professionals using previously established HABS-HD procedures.

Statistical analyses

Statistical analyses were conducted using JASP 0.16.4.

Preliminary analyses

Preliminary independent *t*-tests were conducted to examine ethnoracial group differences on performance in attention/EF and memory. Spearman's correlations were also quantified between multiple variables of interest (composite *z*-scores on attention/EF, composite *z*-scores on memory, age, ICV, WMH), across the whole sample and separately for each ethnoracial group. Additionally, chi-square tests were conducted to examine ethnoracial group differences on CVD risk factors/conditions. Independent *t*-tests were also conducted to examine differences in WMH volumes based on CVD risk factors/conditions.

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Table 2. Descriptive and inferential statistics associated with MRI and neuropsychological variables in the study sample

	MA			NHW					
	n	*M*	*SD*	n	*M*	*SD*	*t*	*p*	*d*
MRI variable									
WMH volume	675	2.38	4.79	660	3.81	6.75	4.47	<.001	0.245
ICV	787	$1.35 \times 10^{+6}$	160438.21	693	$1.46 \times 10^{+6}$	193431.75	12.76	<.001	0.665
Neuropsychological composite z-scores									
Attention/EF	850	−0.09	0.76	747	0.06	0.80	3.91	<.001	0.196
Memory	849	−0.05	0.84	747	0.06	0.91	2.58	.010	0.130

Note: MA = Mexican American, NHW = non-Hispanic White, MRI = magnetic resonance imaging, WMH = white matter hyperintensity (raw values), ICV = intracranial volume.

Primary analyses

For primary analyses, two analysis of covariance (ANCOVA) tests were conducted to examine effects of ethnoracial group, WMH volume, and an ethnoracial group x WMH volume interaction on performance (composite *z*-scores) in (1) attention/EF and (2) memory, while accounting for potential main effects of ethnoracial group and WMH volume in addition to age, sex, and ICV. A Bonferroni correction ($\alpha_{BC} = .05/2 = .025$) was applied to account for multiple ANCOVA tests.

ANCOVA tests were also conducted to examine effects of ethnoracial group, WMH volume, and an ethnoracial group x WMH volume interaction on performance on individual attention/EF and memory tests, while accounting for potential main effects of ethnoracial group and WMH volume in addition to age, sex, and ICV. A Bonferroni correction ($\alpha_{BC} = .05/4 = .0125$) was applied to account for multiple ANCOVA tests.

For η_p^2 effect sizes associated with all ANCOVA tests, values of .001, .006, and .014 were interpreted to represent small, medium, and large effect sizes, respectively (Cohen, 1992).

Post hoc analyses

To further aid interpretation of findings from primary analyses, multiple post hoc analyses were conducted. First, ANCOVA tests were conducted to examine whether ethnoracial group further moderated interactive effects of CVD risk factors/conditions and WMH volume on neuropsychological performance (while accounting for potential main effects of ethnoracial background, CVD risk factors/conditions, and WMH volume in addition to age, sex, and ICV).

Second, a series of post hoc analyses were conducted to examine the potential influence of education (a proxy for cognitive reserve [Livingston et al., 2020]) on observed associations in primary analyses. An independent *t*-test examining ethnoracial group differences on education was conducted. Regression analyses were also conducted to examine associations between education and WMH volume in the whole sample while accounting for age, sex, and ICV. Additionally, an ANCOVA test was conducted to examine whether ethnoracial group moderated associations between education and WMH volume (with main effects estimated for ethnoracial background and education in addition to age, sex, and ICV).

Results

Table 1 includes descriptive and inferential statistics (ethnoracial group differences) associated with demographic and clinical characteristics of the study sample. Table 2 includes descriptive and inferential statistics (ethnoracial group differences) associated with MRI and neuropsychological variables.

Preliminary analyses

Preliminary independent *t*-tests showed that the MA group performed significantly worse than the NHW group in attention/EF ($t[1595] = 3.91$, $p < .001$, $d = 0.196$) (Figure 1a) and memory ($t[1594] = 2.58$, $p = .010$, $d = 0.130$) (Figure 1b). In the whole sample (Figure 1c) and for each of the ethnoracial groups (Supplementary Figure 1), composite *z*-scores for both attention/EF and memory were significantly correlated with age and WMH, and composite *z*-scores for memory (but not attention/EF) were also significantly correlated with ICV. Correlation results supported our examination of differential associations between WMH volume and neuropsychological performance across the two ethnoracial groups in primary analyses. Moreover, the MA and NHW groups showed significant differences in common CVD risk factors/conditions, including consensus diagnoses of hypertension ($\chi^2[N=1598] = 9.74$, $p = .002$), CVD ($\chi^2[N = 1598] = 10.59$, $p = .001$) and diabetes ($\chi^2[N=1598] = 108.56$, $p < .001$) (Table 1). While rates of hypertension and diabetes were significantly higher in the MA group than the NHW group, rates of CVD were significantly higher in the NHW group than the MA group. Furthermore, WMH volumes were significantly higher among those with consensus diagnoses of hypertension ($t[1320] = 7.63$, $p < .001$, $d = 0.431$), CVD ($t[1320] = 4.53$, $p < .001$, $d = 0.478$) and diabetes ($t[1320] = 2.99$, $p = .003$, $d = 0.194$) than those without consensus diagnoses of these CVD risk factors/conditions.

Regarding cognitive status, the majority (78.6%) of study participants (74.7% and 83.0% of MA and NHW participants, respectively) was classified as cognitively normal. However, there were significant differences in cognitive status across ethnoracial groups (χ^2 $[N=1598] = 16.46$, $p < .001$): there were lower proportions of cognitively normal classifications and higher proportions of MCI and dementia classifications in the MA group compared to the NHW group. Given these observed differences in diagnostic classifications across ethnoracial groups and that the majority of the study sample was cognitively normal (thus, a focused analysis with the cognitively normal subsample would be sufficiently powered), primary analyses – in addition to post hoc analyses examining differential associations between education and WMH volume – were first performed using the whole sample, then using a subsample including only (MA and NHW) participants classified as cognitively normal.

Primary analyses: differential associations between WMH volume and neuropsychological performance

Composite z-scores in attention/EF and memory

An ANCOVA test showed a significant ethnoracial background x WMH volume interaction ($F[1,1265] = 15.05$, $p < .001$, $\eta^2 = .011$)

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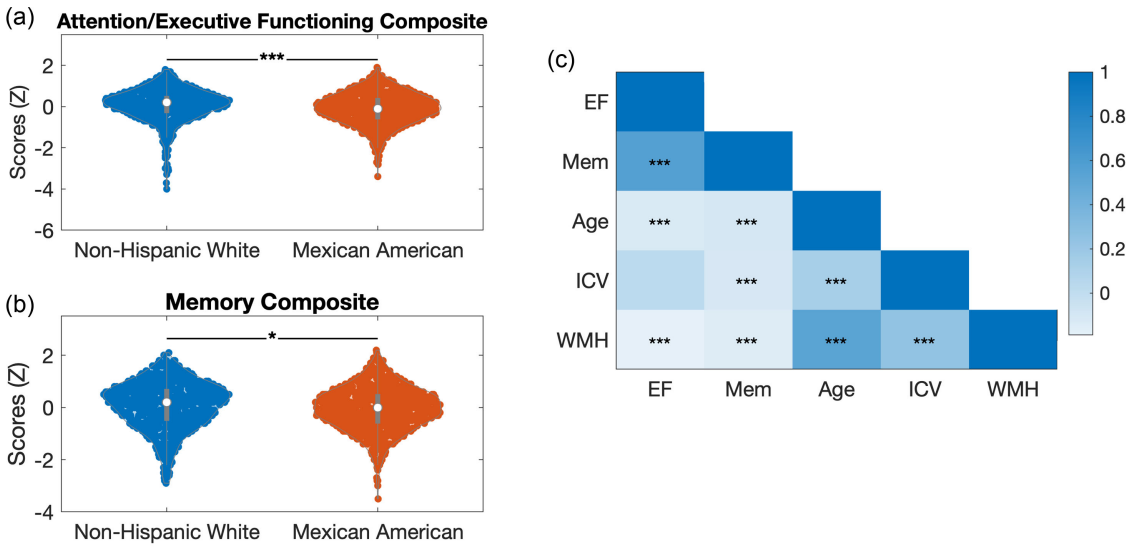

Figure 1. Ethnoracial group differences on composite z-scores for attention/EF (***a***) and memory (***b***), in addition to overall correlations of composite neuropsychological z-scores with age, ICV, and WMH volume (***c***). EF = attention/EF; Mem = memory; ICV = intracranial volume; WMH = white matter hyperintensity.

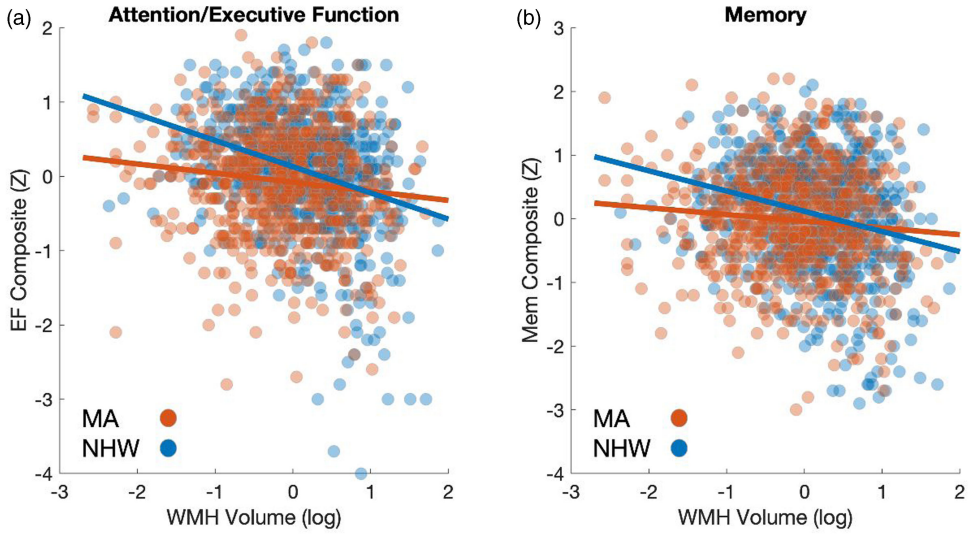

Figure 2. Differential associations between white matter hyperintensity (WMH) volume and neuropsychological performance in the MA and NHW groups for attention/EF (***a***) and memory (***b***). Interactions were assessed while accounting for age, sex, education, and intracranial volume (ICV).

on performance in attention/EF, while accounting for potential main effects of ethnoracial background and WMH volume in addition to age, sex, and ICV (Figure 2a). The interaction reflected a steeper association between WMH and attention/EF in the NHW group compared to the MA group. The ethnoracial background x WMH volume interaction effect on attention/EF was retained (with marginal significance) in the subsample including only cognitively normal participants (F[1,1013] = 3.85, p = .05, η^2 = .004).

An ANCOVA test also showed a significant ethnoracial background x WMH volume interaction (F[1,1264] = 10.77, p = .001, η^2 = .008) on performance in memory, while accounting for potential main effects of ethnoracial background and WMH volume in addition to age, sex, and ICV (Figure 2b). The interaction reflected a steeper association between WMH and memory in the NHW group compared to the MA group. The ethnoracial background x WMH volume interaction effect on memory was not retained in the subsample including only cognitively normal participants (F[1,1012] = 0.81, p > .05, η^2 < .001).

Individual attention/EF and memory tests

An ANCOVA test showed a significant ethnoracial background x WMH volume interaction on multiple individual tests of attention/EF (TMT Part A, Digit Symbol Substitution, and Digit Span, but not TMT Part B) and memory (SEVLT Learning and Logical Memory Immediate and Delayed Recall, but not SEVLT Recall), while accounting for potential main effects of ethnoracial background and WMH volume in addition to age, sex, and ICV (Supplementary Table 1). Interactions reflected steeper associations between WMH and test performance in the NHW group compared to the MA group.

Post hoc analyses

Moderating effects of ethnoracial group on CVD risk factors/conditions x WMH volume interactions on neuropsychological performance

Given (1) significant ethnoracial group differences on neuropsychological performance and CVD risk factors/conditions

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coupled with significant differences in WMH volume based on CVD risk factors/conditions in preliminary analyses, in addition to (2) ANCOVA tests showing differential associations between WMH volume and neuropsychological performance across the MA and NHW groups, we explored whether interactive effects of CVD risk factors/conditions (consensus diagnoses of hypertension, CVD, diabetes) and WMH volume on attention/EF and memory were further moderated by ethnoracial background (while accounting for potential main effects of ethnoracial background, CVD risk factors/conditions, and WMH volume in addition to age, sex, and ICV). These ANCOVA tests showed no significant WMH volume x hypertension x ethnoracial background interaction effects on attention/EF ($F[1, 1261] = 0.53$, $p > .05$, $\eta^2 < .001$) or memory ($F[1, 1260] = 1.15$, $p > .05$, $\eta^2 < .001$). Additionally, there were no significant WMH volume x CVD x ethnoracial background interaction effects on attention/EF ($F[1, 1261] = 0.16$, $p > .05$, $\eta^2 < .001$) or memory ($F[1, 1260] = 0.45$, $p > .05$, $\eta^2 < .001$). Finally, there were no WMH volume × diabetes × ethnoracial background interaction effects on attention/EF ($F[1, 1261] = 0.01$, $p > .05$, $\eta^2 < .001$) or memory ($F[1, 1260] = 0.09$, $p > .05$, $\eta^2 < .001$).

Differential associations between education and WMH volume

In the primary analyses, we observed differential associations between WMH volume and neuropsychological performance across the two ethnoracial groups, wherein the associations were steeper in the NHW group than in the MA group. We next sought to examine whether participants' educational background (viz., years of education), a widely used proxy of cognitive reserve (Livingston et al., 2020), could partially account for these differential associations. A post hoc independent *t*-test showed that the MA group completed significantly fewer years of education compared to the NHW group ($t[1596] = 31.88$, $p < .001$, $d = 1.599$) (Table 1), although the MA group appeared to have more variability in educational level. Regression analyses showed a significant negative association between education and WMH volume across the whole sample ($B = -0.01$, $SE < 0.01$, $p = .014$, 95% CI [−0.016, −0.002]), while accounting for age, sex, and ICV. However, an ANCOVA test revealed a significant ethnoracial background x education interaction effect on WMH volume ($F[1,1266] = 7.47$, $p = .006$, $\eta^2 = .004$), with main effects estimated for ethnoracial background and education in addition to age, sex, and ICV. This interaction effect was retained in the subsample of cognitively normal participants ($F[1,1013] = 5.65$, $p = .018$, $\eta^2 = .004$).

Discussion

The aim of the present study was to examine potential interactive effects of ethnoracial background and WMH volume on neuropsychological performance in MA and NHW adults in the HABS-HD cohort. Key findings demonstrated differential associations between WMH and neuropsychological performance across the two groups, wherein negative associations between WMH volume and neuropsychological performance were steeper for NHW participants than for MA participants; these were medium-sized effects. When analyses were restricted to a subsample of participants classified as cognitively normal, the ethnoracial background x WMH volume was retained (with marginal significance) for attention/EF, but not memory, further highlighting a robust influence of WMH on attention/EF, particularly for NHW adults. The present findings extend those from previous research showing that higher WMH volume is associated with worse performance in executive functioning in NHW adults and other ethnoracial groups (Brickman et al., 2011; Debette & Markus, 2010; Dong et al., 2010; Stavitsky et al., 2010), but are in contrast with recent findings showing significant associations in MA individuals (Vintimilla et al., 2021). Specifically, the present findings highlight that while pathological changes in the form of WMH may negatively impact neuropsychological outcomes for some ethnoracial groups, including NHW adults, this effect appears to be less robust or consistent for MA adults. Nevertheless, it is critical to acknowledge that previous work validating increased WMH volume as a marker of CVD risk and pathology was done with ethnoracially homogeneous (primarily NHW) samples, and it is possible that WMH volume does not adequately capture aspects of white matter disease that are relevant for MA and other Latino populations. Additional research examining the validity and utility of various white matter indices with these and other ethnoracially diverse populations is needed.

WMH volumes were higher in individuals with consensus diagnoses of hypertension, CVD, or diabetes, in agreement with earlier findings (Henskens et al., 2009; Moroni et al., 2018; Wang et al., 2020). Additionally, there were higher rates of hypertension and diabetes among MA participants compared to NHW participants, although there were higher rates of CVD among NHW participants compared to MA participants, consistent with other research showing higher rates of CVD risk factors, but lower rates of total CVD, among Latino individuals (Graham, 2015; Liao et al., 1997; Mensah et al., 2005; Mitchell et al., 1990). Nevertheless, post hoc analyses were conducted to examine whether ethnoracial background moderated the observed interactive effects of CVD risk and WMH on cognition. These analyses demonstrated no significant interactions among ethnoracial background, CVD risk, and WMH on performance in attention/EF or memory. Taken together, these findings suggest that while there appears to be a clear association between CVD risk and pathological changes in the form of WMH for NHW adults, it is difficult to conclude that a nonsignificant association between WMH volume and neuropsychological performance among MA adults could be attributable to ethnoracial group differences in overall CVD risk, at least in the present study sample. However, it is possible that higher rates of clinically diagnosed CVD in the NHW group, specifically, partially explain the observed differential associations between WMH volume and neuropsychological performance across the two ethnoracial groups.

We also explored the potential influence of education on the observed differential associations between WMH and neuropsychological performance in the MA and NHW groups. It is well-documented that education plays an integral role in facilitating cognitive reserve and that higher educational attainment in turn reduces dementia risk (Livingston et al., 2020; Stern, 2012; Stern et al., 2020). Moreover, research has shown that for any given level of cognitive functioning, individuals with higher reserve can have more brain pathology in the form of WMH, suggesting that they may better cope with the effects of neuronal damage than those with lower reserve (Brickman et al., 2011). Post hoc analyses in the present study revealed that the MA group completed fewer years of education compared to the NHW overall. However, the MA group appeared to have more variability in educational attainment. Additionally, lower educational attainment has been shown to drive racial and ethnic disparities in dementia risk (Rodriguez et al., 2018; Santamaria-Garcia et al., 2023; Zahodne et al., 2021). Notably, the present study showed that higher educational

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attainment corresponded to lower WMH volume in the NHW group, whereas no association was observed in the MA group (and this effect was retained in analyses restricted to participants classified as cognitively normal). Furthermore, it is worth noting that the MA group in the present study performed worse on attention/EF and memory relative to the NHW group. Taken together, our findings suggest that for aging NHW adults, the impact of WMH on performance in attention/EF (and memory) may be mitigated by cognitive reserve related to educational attainment and that aging MA adults may be less likely to benefit from these buffering effects of education due to lower average educational attainment. Other research has demonstrated that even for ethnoracial minorities (e.g., Latino and African American individuals) with lower educational attainment, every additional year of education decreases the risk of dementia (by a hazard ratio of 0.95 [Rodriguez et al., 2018]). Moreover, while Latino adults may perform worse than NHW adults at baseline, they may show similar or slower trajectories of cognitive decline (Kezios et al., 2023). Thus, identifying ways to improve educational attainment and quality among MA and other ethnoracial minority groups may be imperative in efforts to promote cognitive and brain health in these populations. It is also worth noting that the MA group was younger than the NHW group. Nevertheless, we accounted for age in our analyses, and it is unlikely that age-related differences drove any observed effects on neuropsychological outcomes in the present study.

A notable strength of the present study was its inclusion of and emphasis on a MA subsample that represents a growing portion of the US population that has high CVD and ADRD risk (Kulshreshtha et al., 2019; Matthews et al., 2019), yet remains underrepresented in and underserved by cognitive aging research. An additional strength was the use of composite neuropsychological *z*-scores, which have been shown to provide reliable metrics of cognitive domain functioning in studies using MRI techniques to examine neural correlates of cognitive decline (Amaefule et al., 2021).

Nevertheless, the present study is not free of limitations. First, the study focuses on a US MA cohort, which limits the generalizability of our findings to other Latino groups. Second, the cross-sectional design precludes us from establishing causation with our findings. That is, additional factors related to WMH, including but not limited to other CVD risk factors and social determinants of health, may be partially driving the observed differential effects of white matter changes on neuropsychological outcomes in the MA versus NHW groups. For example, data on length of US residency and education quality among MA participants may provide some insight into the potential influence of acculturation (above and beyond educational attainment) on our findings. Similarly, additional mechanisms in the brain such as the extent of redundancy (Sadiq et al., 2021) and resilience in large-scale cognitive networks (Stanford et al., 2022) may contribute to the lack of an observed association between WMH and neuropsychological performance in the MA group. These could be more formally tested in future research. Moreover, future studies with larger samples would benefit from directly examining a three-way WMH x education x ethnoracial background interaction on neuropsychological outcomes. Furthermore, it is worth reiterating that WMH volume may not adequately capture aspects of white matter disease that are relevant for MA and other Latino populations, and future research should more thoroughly investigate the validity and utility of various white matter indices with these and other ethnoracially diverse populations. Finally, future studies with available data should directly examine the potential influences of other sociocultural and psychosocial factors on associations between WMH volume and neuropsychological performance in MA and other ethnoracial minority groups.

In sum, we found evidence for differential associations between WMH volume and neuropsychological performance across ethnoracial groups, wherein negative associations were steeper for NHW versus MA participants. The present findings have important clinical implications. Notably, for patients in whom cerebral white matter disease is detected, promoting preventative lifestyle changes, including dietary lifestyle modification may improve cardiovascular health and in turn mitigate declines in cognitive and brain health. Additional studies with larger and more diverse Latino samples, longitudinal data, more comprehensive CVD, sociocultural, and psychosocial indices, and more thorough investigation of the validity and utility of white matter indices as markers of CVD risk and pathology in these populations, are needed to further elucidate our understanding of associations between WMH and cognitive decline in MA and other Latino groups with high CVD and ADRD risk.

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