Title

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Journal

Alzheimer's & Dementia Diagnosis Assessment & Disease Monitoring, 13(1)

ISSN

2352-8729

Authors

Vintimilla, Raul
Hall, James
King, Kevin
et al.

Publication Date

2021

DOI

10.1002/dad2.12236

Received: 8 February 2021 | Revised: 22 July 2021 | Accepted: 3 August 2021 | Published online: 11 October 2021

DOI: 10.1002/dad2.12236

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

MRI biomarkers of small vessel disease and cognition: A cross-sectional study of a cognitively normal Mexican American cohort

Raul Vintimilla[1] | **James Hall**[1] | **Kevin King**[2] | **Meredith N. Braskie**[3] | **Leigh Johnson**[1] | **Kristine Yaffe**[4] | **Arthur W. Toga**[3] | **Sid O'Bryant**[1] | **The Health and Aging Brain Study (HABS-HD) Study Team**[#]

[1] University of North Texas Health Science Center, Fort Worth, Texas, USA

[2] Barrow Neurological Institute, Phoenix, Arizona, USA

[3] University of Southern California, Los Angeles, California, USA

[4] University of California San Francisco, San Francisco, California, USA

Correspondence
Raul Vintimilla, Institute for Translational Research, University of North Texas Health Science Center, 855 Montgomery Street, Fort Worth, TX, 76123 USA.
Email: raul.vintimilla@unthsc.edu

[#]HABS-HD MPIs: Sid E O'Bryant, Kristine Yaffe, Arthur Toga, Robert Rissman, & Leigh Johnson; and the HABS-HD Investigators: Meredith Braskie, Kevin King, James R Hall, Melissa Petersen, Raymond Palmer, Robert Barber, Yonggang Shi, Fan Zhang, Rajesh Nandy, Roderick McColl, David Mason, Bradley Christian, Nicole Philips, Stephanie Large, and Rocky Vig.

Funding information
National Institute on Aging; National Institutes of Health, Grant/Award Numbers: R01AG054073, R01AG058533

Abstract

Background: The current project sought to evaluate the impact that white matter hyperintensities (WMH) have on executive function in cognitively normal Mexican Americans, an underserved population with onset and more rapid progression of dementia.

Methods: Data from 515 participants (360 female) enrolled in the Health and Aging Brain Study: Health Disparities project were analyzed. Participants underwent clinical evaluation, cognitive testing, and a brain MRI. Linear regression was used to predict the effect of total WMH volume on cognitive test scores. Age, sex, and education were entered as covariates.

Results: Regression analysis showed that WMH volume significantly predicted executive function. WMH also predicted global cognition and attention scores, although not significantly after adjusting for age.

Conclusion: In this sample of cognitively normal Mexican Americans, we found that WMH volume was associated with lower scores in a measure of executive function, after accounting for age, sex, and education.

KEYWORDS
cardiovascular risk factors, cerebral small vessel disease, cognition, Mexican American, MRI

1 | INTRODUCTION

Cardiovascular disease (CVD) and cardiovascular risk factors (CVRFs), such as hypertension, dyslipidemia, obesity, and smoking, play a relevant role in the etiology of Alzheimer's disease (AD).[1] With the exception of dyslipidemia, these risk factors have been shown to promote brain small vessel disease (SVD) which has been linked to both vascular dementia and AD.[2,3]

Imaging techniques such as magnetic resonance imaging (MRI) have become widely available and are increasingly used in clinical settings. White matter hyperintensities (WMH), lacunae, and microbleeds are common features of brain SVD assessed by MRI.[4] WMH are a common

incidental finding. In a comprehensive systematic review and meta-analysis, Debette et al. reported that 20% of adults around 60 years of age showed WMH, and the prevalence goes up to 94% by age 80.[5] The presence of WMH has been associated with an increased risk of stroke, dementia, and death. Although many individuals with WMH are asymptomatic, a link between WMH and a decline in global cognition, executive function, and processing speed has been suggested.[5] Many studies have found an association between baseline WMH volume and longitudinal changes in executive function.[6,7] Specifically, research that used voxel-based lesion-symptom mapping showed a particular association among the damage at subcortical-frontal connections and executive function.[8]

Studies have shown that the relationship between WMH and cognitive impairment differs across race and ethnicity groups. When compared with non-Hispanic Whites, African Americans and Hispanics had larger WMH volumes and worse performance on cognitive tests.[9,10] Hispanics are the largest minority in the United States, and Hispanics of Mexican origin account for almost 65% of this population.[11] In a review of CVD in Latinos in the United States, Balfour et al.[12] reported that Mexican Americans (MAs) have a worse vascular risk profile relative to non-Hispanic Whites: Specifically, they have a higher prevalence of obesity, higher levels of total and low-density lipoprotein cholesterol levels, lower high-density lipoprotein cholesterol levels, and higher prevalence of diabetes. MAs also have an earlier onset and faster progression of dementia.[13,14] Thus, continued research on MRI markers of SVD and its association with cognition in this segment of the population is warranted.

We hypothesized that in a sample of community-dwelling cognitively normal MAs, higher volumes of WMH will have an impact on cognition, specifically on executive function. To test our hypothesis, we examined the effect of total WMH load, assessed by quantitative MRI analysis, on multiple cognitive domains. We also assessed whether other MRI markers of SVD, such as lacunae and microbleeds, modulate this effect. This study provides an opportunity to add to the limited literature available regarding the relationship of WMH and cognition in MAs,[15,16] and to better understand how WMH affect different cognitive domains in this population.

RESEARCH IN CONTEXT

1. **Systematic review**: To evaluate the current state of research examining the association of white matter hyperintensities (WMH) and cognition, we conducted a literature review. We also reviewed prior work looking at the effects of WMH on cognition in Mexican Americans (MAs), although studies in this population are lacking.
2. **Interpretation**: WMH were found to be associated with lower scores in measures of global cognition, attention, and executive function in an MA sample. After accounting for age, sex, and education, only the effects on executive function remained significant.
3. **Future directions**: This work seeks to add to the limited literature regarding WMH and cognition in MAs, and to better understand how WMH affect cognitive domains in this underserved population. Results from this type of study could drive future prevention interventions with public health impact potential.

HIGHLIGHTS

- Mexican Americans have a worse cardiovascular risk profile that non-Hispanic Whites.
- Mexican Americans have an early onset and faster progression of dementia.
- White matter hyperintensities (WMH), related to cardiovascular risk factors, are associated with cognitive decline.
- In our study, WMH were associated with lower performance in executive function in Mexican Americans.
- Ethnicity should be taken in account for risk factor interventions planning.

2 | METHODS

2.1 | Study design and setting

We conducted a cross-sectional analysis of data from an ongoing longitudinal study at the University of North Texas Health Science Center. The Health and Aging Brain Study: Health Disparities (HABS-HD) has been recruiting participants since 2017 under the North Texas Regional IRB approval. Each participant, and/or legal representative for cognitively impaired persons, signs a written informed consent. The HABS-HD study uses a community participatory research approach and recruitment methodology. Recruitment consists of community recruiters, community presentations, flyers/brochures, door-to-door recruitment, newspaper advertisement, and snowball recruitment. To target MAs, analysis of ZIP codes in Tarrant County with the highest population of Hispanic individuals was performed to determine locations for recruitment. Subjects included in the study had an age of 50 and above, a self-reported ethnicity of MA or non-Hispanic White, and were willing and capable to provide blood samples and undergo neuroimaging studies. Considering the nature of the disease, and its possible impact on cognition, individuals with type 1 diabetes, cancer diagnosis, chemotherapy or radiotherapy in the last 12 months, severe mental illness, traumatic brain injury with loss of conscience in the last 12 months, active infection, alcohol/substance abuse, and other severe illness such as end stage renal failure or chronic heart failure, are excluded from participation on the HABS-HD study.

HABS-HD participants undergo a clinical interview, neuropsychological assessment, functional examination, MRI of the head, and blood draw for clinical and biomarker analysis. An informant interview is

conducted to assess functional level. All components are completed during a baseline visit and every 24 months during follow-up visits.

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

A weekly consensus review of experienced clinicians assign a cognitive diagnosis based on the Clinical Dementia Rating Scale (CDR), self-report and informant questionnaires, and neuropsychological tests scores. Based on previous published criteria by O'Bryant et al.[17] a CDR sum of boxes ≥ 2.5 and a cognitive test z-score equal to two standard deviations or below the mean on two or more tests is required for a dementia diagnosis. A diagnosis of mild cognitive impairment (MCI) is assigned based on complaints of cognitive changes by self or other, a CDR sum of boxes of 0.5 to 2.0, and at least one cognitive test with a z-score equal to or below 1.5 standard deviations. Participants who perform within normal parameters on psychometric testing and have a CDR = 0 are classified as cognitively normal.

2.2 | Study population

From March 2017 until October 2019, 1357 subjects were enrolled in the study baseline visit. In order to analyze the relationship of WMH and cognition within a cognitively normal sample of MA elders, we excluded 181 participants with a diagnosis of MCI, and 76 participants with an AD diagnosis. Of the remaining 1100 subjects, 515 self-identified as MA. The final sample was composed of 515 cognitively normal subjects. One hundred and forty-eight subjects (28.7%) who were diagnosed as cognitively normal reported subjective memory complaints. All subjects included in the final analysis met the following criteria: (1) having undergone at least partial neuropsychological evaluation, and having a cognitive diagnosis at the time of their MRI, (2) not meeting criteria for MCI or dementia, (3) self-reporting their ethnicity as MA, (4) having complete data on all covariates (ie, age, sex, education), (5) having complete data on quantitative MRI variables of interest (ie, WMH volume, intracranial volume [ICV], presence of lacunae, and/or microbleeds).

2.3 | MRI acquisition

MRI data were acquired using a 3T SKYRA scanner (Siemens Healthineers AG; Erlangen, Germany) using the same protocol for all participants. T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE; repetition time = 2300 ms, echo time = 2.93 ms, field of view = 270, matrix = 256 with 1.2 mm slice thickness, and voxel size = 1.1 mm x 1.1 mm x 1.2 mm), and T2-weighted fluid attenuated inversion recovery (FLAIR; repetition time = 4.800 ms, echo time = 441 ms, TI time = 1650 ms, field of view = 256, matrix = 256 with slice thickness = 1.2 mm, and voxel size = 1.0 mm x 1.0 mm x 1.2 mm) images were acquired in the sagittal plane.

2.4 | Predicting variables

Due to non-normality, WMH volume values were log transformed. To adjust for individual cranial size differences, the residual approach was used.[18] This method involves running a linear regression model using ICV as the independent predictor, and the region of interest (log transformed WMH volume) as the dependent variable. We used the residual values of this regression (log transformed WMH volume adjusted by ICV) to predict tests scores among cognitively normal participants.

WMH volume was measured from the MPRAGE and FLAIR images using the Statistical Parametric Mapping Lesion Segmentation Toolbox Lesion Growth Algorithm (www.statisticalmodelling.de/lst.html).[19] Estimated ICV was derived from Freesurfer v6.0 analysis of the T1 MPRAGE data (http://surfer.nmr.mgh.harvard.edu/).[20] Lacunae and microbleeds (hemosiderin deposits) were detected and counted by a neuroradiologist (KK), were reported as "absent" or "present," and used to predict test scores.

2.5 | Cognitive function

The Mini-Mental State Examination (MMSE) was used to assess global cognition.[21] The Trail Making Test, parts A and B, were used as measures of attention and executive function, respectively.[22] Verbal fluency (phonetic and semantic) were assessed with the FAS and animal naming tests.[23] The Spanish English Verbal Learning Test (SEVLT) evaluated immediate and delayed memory.[24] The Digit-Symbol Substitution Test (DSST)[25] ascertained processing speed.

2.6 | Covariates

Demographic information including age, gender, and total years of education as reported during the interview were covariates.

2.7 | Statistical analysis

Data were analyzed with SPSS version 25 for Windows (SPSS INC., Chicago, IL). To normalize WMH distribution, we used a log transformation, adjusted by ICV. Lacunae and microbleeds were entered in the models as categorical variables (0 = absent, 1 = present). With the exception of MMSE, neuropsychological test raw scores were transformed into z-scores to facilitate effect size comparisons between variables. To make test scores more comparable across tests, the signs of the z-scores for all tests for which a higher score indicated a worse outcome were inverted before statistical comparisons with imaging

measures were performed. After this transformation, a higher number indicated a better score for all neuropsychological tests.

First, three multiple linear regression analyses were conducted to estimate B coefficients and 95% confidence intervals for the association among WMH, lacunae, and microbleeds, with each cognitive test score as a separate outcome. Then, we conducted a regression model to analyze the relation between WMH and the cognitive scores, using lacunae and microbleeds as covariates. The second set of analyses examined the relation of total WMH volume with cognition, with each test score as a separate outcome, and this time we included sex, age, and education as control variables in the regression models. Statistical significance was set to $P \leq .05$.

3 | RESULTS

3.1 | Characteristics of the study population at the time of MRI

The total sample included 515 cognitively normal participants with a mean age of 62.6 years (SD 7.7); 69.9% of the participants were female, and had a mean of 9.8 years (SD 4.5) of education. A summary of the demographic, CVRF, tests score, and neuroimaging characteristics of the sample is given in Table 1.

3.2 | Regression analysis

The results of the regression analysis for the entire sample are shown in Table 2. Regression models showed that WMH volume significantly predicted MMSE (B = −0.43 (−0.76 to−0.10), $P = .001$), Trails B (B = −0.16 (−0.27 to −0.06), $P = .002$), and DSST (B = −0.12 (−0.22 to −0.02), $P = .01$) scores. The results remained significant after adjusting for sex and education, but the MMSE and DSST scores were no longer significant after adjusting for age ($P > .05$). The presence of subjective memory complaints did not modify the associations. Lacunae and microbleeds did not influence the results when entered as confounding variables to the models. Neither lacunae nor microbleeds showed a significant relation with cognitive scores when used as the independent variable in the regression models. Because of the small sample sizes for lacunae (n = 22) and microbleeds (n = 53), a low statistical power reduced the chance of detecting an effect.

4 | CONCLUSIONS

In this sample of community-based cognitively normal MAs we found the following: (1) WMH load was significantly associated with executive function scores; (2) WMH load was also associated with global cognition and processing speed scores, but this association was no longer significant after adjusting for age; (3) lacunae and microbleeds, independently, were not associated with any cognitive scores, as neither

TABLE 1 Characteristics of the study population

Characteristic[a]	N = 515
Age	62.6 (7.76)
Sex (% female)	69.9 (N = 360)
Education, years	9.8 (4.5)
Hypertension (% yes)	61.3 (N = 316)
Diabetes Mellitus (% yes)	35.7 (N = 184)
Dyslipidemia (% yes)	63.6 (N = 328)
Obesity (% yes)	48.3 (N = 249)
Subjective memory complains (% yes)	28.7 (N = 148)
MMSE	26.9 (2.77)
Trails A	0.19 (0.68)
Trails B	0.22 (0.82)
FAS	0.14 (0.90)
Animal naming	0.14 (0.87)
SEVLT immediate	0.21 (0.83)
SEVLT delayed	0.31 (0.76)
DSST	0.16 (0.83)
Total WMH volume	2.17 (4.44)
Total WMH volume, after logarithm[b]	0.77 (0.74)
Total ICV (mL)	1374.87 (154.95)
Total log WMH volume (adjusted by ICV)[c]	−0.042 (0.72)
Lacunae (% yes)	4.3% (N = 22)
Microbleeds (% yes)	10.3 (N = 53)

Abbreviations: DSST, Digit-Symbol Substitution Test; ICV, intracranial volume; MMSE, Mini-Mental State Examination; SEVLT, Spanish English Verbal Learning Test; WMH, white matter hyperintensities.
[a]Mean (SD) unless otherwise specified.
[b]Logarithm, base 10.
[c]WMH log value adjusted by ICV (unstandardized residual).

TABLE 2 Linear regression: WMH and neuropsychological test scores

	B	95% CI	t	P
Trails A	0.01	−0.07 to 0.09	0.28	.77
Trails B	−0.16	−0.27 to −0.06	−3.14	.002[a]
FAS	−0.01	−0.12 to 0.09	−0.19	.84
Animals	0.00	−0.09 to 0.11	0.13	.89
SEVLT Immediate	−0.05	−0.16 to 0.04	−1.15	.25
SEVLT Delayed	−0.04	−0.14 to 0.04	−0.98	.32
DSST	−0.12	−0.22 to −0.02	−2.46	.01[b]
MMSE	−0.43	−0.76 to −0.10	−0.11	.01[b]

Abbreviations: DSST, Digit-Symbol Substitution Test; MMSE, Mini Mental State Examination; SEVLT, Spanish English Verbal Learning Test, WMH, white matter hyperintensities.
[a]Remains significant after controlling for age, sex, and education.
[b]Not significant after controlling for age.

MRI marker affected the results when entered as a confounder; and (4) sex and education did not influence the results.

This association between WMH and worse performance in executive function is consistent with many studies,[26,27] and suggests a relationship between WMH and cortical frontal system involvement.[28] Executive functions are closely related to cortical-subcortical circuits passing along the white matter, so any damage to the white matter can potentially disrupt these circuits.[5] Tullberg et al. concluded in their research that regardless of WMH location on the brain, they were associated with frontal and executive dysfunction.[29] Recently, Camerino et al. provided, for the first time, evidence that WMH in the thalamic radiations, caudate nuclei, and corpus callosum are associated with worse performance in executive function and language in dementia-free subjects.[30] Consistent with our findings, age did not affect the association of WMH and executive function.[31]

Low performance in processing speed,[32,33] memory,[15,34] language,[35] and global cognition tasks[28,36] have been related to WMH, which is contrary to our results. In agreement with our findings, other researchers reported no association between WMH and processing speed,[29] memory,[37] or global cognition.[27] These discrepancies may be explained in part by differences in methodology and study design, including different mean ages of the participants, the fact that the subjects in other studies were predominantly non-Hispanic Whites, different neuropsychological tests used, the use of composite scores, MRI protocols, image processing, and most importantly, the use of regional WMH volumes instead of total volumes in the majority of the studies. It is possible that WMH at strategic regional tracts have a different impact on specific cognitive domains. A study of the ALFA (for ALzheimer's and FAmilies) cohort demonstrated the importance of periventricular and deep WMH load. The authors found that deep WMH lesions were strongly linked to memory and executive function.[25] Another explanation for the conflicting results may be cortical atrophy mediation. Specifically, for memory impairment, He et al. concluded that gray matter is more important than WMH.[38] Rizvi et al. also suggested that SVD promotes neurodegenerative changes, so in the end atrophy, and not WMH, is responsible for cognitive decline.[10]

Contrary to previous research,[39–41] lacunae and microbleeds were not associated with cognitive performance in our cohort. It is likely that the low number of individuals with these pathologies in the cohort did not allow enough power to show significant results.

Overall, our study supports the scarce body of literature focusing on the impact of brain SVD on cognition in MAs and extends previous studies done in the older population to middle age adults. These findings are very important because detecting WMH at a younger age may open a window for interventions for secondary prevention at an earlier stage. Key strengths of the study are the community-based sampling of MA men and women who did not have dementia or mild cognitive impairment. Not including cohorts of different Hispanic ethnicities, which may have different risk and genetic factors, makes it easier to detect effects if they exist. Other strengths include the availability of several validated tests for cognitive measures at the time of MRI imaging, the use of high resolution MRI, and automated quantification measures for MRI analysis, removing user bias. Lastly, using WMH as a continuous measure, instead of categories, increased the power to detect associations with cognitive measures.

The study has several limitations. First, the cross-sectional design does not allow us to establish causation. Possibly WMH influence cognition, but possibly other factors related to WMH, such as hypertension or diabetes, are actually driving the cognitive effect. Detailed CVRF data were not available for examining these important effect modifications. The HABS-HD study is longitudinal, so these findings will be reexamined as more data become available. Second, the analyzed data were from an MA cohort, which may limit the generalizability of our findings. Finally, we utilized global WMH volumes for analysis; further research using multiple region volumes may provide a clearer picture of the effects of WMH on specific cognitive domains. Furthermore, we did not analyze other factors that might mediate the relationship between WMH and cognition such as apolipoprotein E (*APOE*) ε4 carrier status, cortical atrophy, hippocampal volume, and lifestyle habits.[42] Future research is needed to determine if the effects of global and regional WMH volumes on cognition are mediated by cortical atrophy, hippocampal volume, *APOE* ε4 status, and lifestyle habits.

In this community-based sample of MA adults, we found that global WMH volume was associated with lower scores in a measure of executive function, after accounting for age, sex, and education. Our results suggest that even low volumes of WMH in middle-aged and older adults can be clinically important. Because of the great potential public health impact, future prevention interventions should focus on these "younger" groups.

CONFLICT OF INTEREST

Sid O'Bryant has multiple patents in neurodegenerative diseases and is the founding scientist for Cx Precision Medicine, Inc. Sid O'Bryant has received grants from the Michael J Fox Foundation. Leigh Johnson owns an interest in Cx Precision Medicine, Inc. Meredith Braskie has received payments for teaching at the University of Southern California where she also receives a stipend for her role as Director of Education at the Stevens Neuroimaging and Informatics Institute. Kristine Yaffe has received grants from the NIH, Department of Defense, Alzheimer's Drug Discovery Foundation, and Doris Duke Foundation. Kristine Yaffe has participated on the Data Safety Monitoring Board or Advisory Board of NIA and Ely Lilly, she also has a role at Alector Inc. Kristine Yaffe has received support for attending AAIC, Beeson, and NIH conferences. Raul Vintimilla, James Hall, Kevin King, and Arthur W. Toga report no conflict of interest.

REFERENCES

1. de Brujin R, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med*. 2014;12:130.
2. Knopman DS, Roberts R. Vascular risk factors: imaging and neuropathologic correlates. *J Alzheimers Dis*. 2010;20(3):699-709.
3. Kerola T, Kettunen R, Nieminen T. The complex interplay of cardiovascular system and cognition: how to predict dementia in the elderly? *Int J Cardiol*. 2011;150(2):123-129.
4. Benjamin P, Zeestraten E, Lambert C, et al. Progression of MRI markers in cerebral small vessel disease: sample size considerations for clinical trials. *J Cereb Blood Flow Metab*. 2016;36(1):228-240.

5. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
6. Jokinen H, Kalska H, Ylikoski R, et al. Longitudinal cognitive decline in subcortical ischemic vascular disease – the LADIS Study. *Cerebrovasc Dis*. 2009;27:384-391.
7. Mungas D, Harvey D, Reed BR, et al. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*. 2005;65:565-571
8. Biesbroek JM, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. *Clin Sci*. 2017;131(8):715-728.
9. Zahodne LB, Manly JJ, Narkhede A, et al. Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. *Curr Alzheimer Res*. 2015;12(7):632-639.
10. Rizvi B, Narkhede A, Last BS, et al. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiol Aging*. 2018;64:25-32.
11. Pew ResearchCenter. How the Hispanic Population is Changing. September 18, 2017. https://www.pewresearch.org/fact-tank/2017/09/18/how-the-u-s-hispanic-population-is-changing
12. Balfour PC Jr, Ruiz JM, Talavera GA, Allison MA, Rodriguez CJ. Cardiovascular disease in Hispanics/Latinos in the United States. *J Lat Psychol*. 2016;4(2):98-113.
13. O'Bryant SE, Johnson L, Reisch J, et al. Risk factors for mild cognitive impairment among Mexican Americans. *Alzheimers Dement*. 2013;9(6):622-631.e1.
14. O'Bryant SE, Johnson L, Balldin V, et al. Characterization of Mexican Americans with mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*. 2013;33(2):373-379.
15. Petkov CI, Wu CC, Eberling JL, et al. Correlates of memory function in community-dwelling elderly: the importance of white matter hyperintensities. *J Int Neuropsychol Soc*. 2004;10:371-381.
16. Wu CC, Mungas D, Petkov CI, et al. Brain structure and cognition in a community sample of elderly Latinos. *Neurology*. 2002;59(3):383-391. https://doi.org/10.1212/WNL.59.3.383.
17. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's Research Consortium study. *Arch Neurol*. 2008;65(8):1091-1095.
18. O'Brien LM, Ziegler DA, Deutsch CK, Frazier JA, Herbert MR, Locascio JJ. Statistical adjustments for brain size in volumetric neuroimaging studies: some practical implications in methods. *Psychiatry Res*. 2011;193(2):113-122.
19. Schmidt P, Gaser C, Arsic M, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *Neuroimage*. 2012;59(4):3774-3783.
20. Buckner RL, Head D, Parker J, et al. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage*. 2004;23(2):724-738.
21. Gluhm S, Goldstein J, Loc K, Colt A, Liew CV, Corey-Bloom J. Cognitive performance on the Mini-Mental State Examination and the Montreal Cognitive Assessment across the healthy adult lifespan. *Cogn Behav Neurol*. 2013;26(1):1-5.
22. Linàs-Reglà J, Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Toorents Rodas D, Garre-Olmo J. The Trail Making Test. *Assessment*. 2017;24(2):183-196.
23. Morelli NL, Cachioni M, Lopes A, et al. Verbal fluency in elderly with and without hypertension and diabetes from the FIBRA study in Ermelino Matarazzo. *Dement Neuropsychol*. 2017;11(4):413-418.
24. González HM, Mungas D, Haan MN. A verbal learning and memory test for English- and Spanish-speaking Older Mexican-American adults. *Clin Neuropsychol*. 2002;16:439-451.
25. Amaresha A, Danivas V, Shivakumar V, et al. Clinical correlates of parametric digit-symbol substitution test in schizophrenia. *Asian J Psychiatr*. 2014;10:45-50.
26. Brugulat-Serrat A, Salvadó G, Sudre CH, et al. Patterns of white matter hyperintensities associated with cognition in middle-aged cognitively healthy individuals. *Brain Imaging Behav*. 2020;14:2012-2023.
27. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. *Neurology*. 2014;82:2127-2138.
28. Au R, Massaro JM, Wolf PA, et al. Association of white matter hyperintensity volume with decrease cognitive functioning: the Framingham Heart Study. *Arch Neurol*. 2006;63:246-250.
29. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. *Neurology*. 2004;63(2):246-253.
30. Camerino I, Sierpowska J, Reid A, et al. White matter hyperintensities at critical crossroads for executive function and verbal abilities is small vessel disease. *Hum Brain Mapp*. 2021:42(4):993-1002.
31. Garnier-Crussard A, Bougacha S, Wirth M, et al. White matter hyperintensities across the adult lifespan: relation to age, Aβ load, and cognition. *Alzheimers Res Ther*. 2020;12:127.
32. Papp KV, Kaplan RF, Springate B, et al. Processing speed in normal aging: effects of white matter hyperintensities and hippocampal volume loss. *Neuropsychol Dev Cogn B*. 2014;21(2):197-213.
33. Luo X, Jiaerken Y, Yu X, et al. Affect of APOE on information processing speed in non-demented elderly population: a preliminary structural MRI study. *Brain Imaging Behav*. 2017;11(4):977-985.
34. Kim JH, Hwang KJ, Kim JH, Lee YH, Rhee HY, Park KC. Regional white matter hyperintensities in normal aging, single domain amnestic mild cognitive impairment, and mild Alzheimer's disease. *J Clin Neurosci*. 2011;18(8):1101-1106.
35. Tubi MA, Feingold FW, Kothapalli D, et al. White matter hyperintensities and their relationship to cognition: effects of segmentation algorithm. *Neuroimage*. 2020;206:116327.
36. Sudo FK, Alves CE, Alves GS, et al. White matter hyperintensities, executive function and global cognitive performance in vascular mild cognitive impairment. *Arq Neuro-Psiquiatr*. 2013;71(7):431-436.
37. Shenkin SD, Bastin ME, Macgillivray TJ, et al. Cognitive correlates of cerebral white matter lesions and water diffusion tensor parameters in community-dwelling older people. *Cerebrovasc Dis*. 2005;20(5):310-318.
38. He J, Wong VS, Fletcher E, et al. The contributions of MRI-based measures of gray matter, white matter hyperintensity, and white matter integrity to late-life cognition. *Am J Neuroradiol*. 2012;33(9):1797-1803.
39. Smith EE, O'Donnell M, Dagenais G, et al. Early cerebral small vessel disease and brain volume, cognition, and gait. *Ann Neurol*. 2015;77(2):251-261.
40. Warren MW, Weiner MF, Rossetti HC, McColl R, Peshock R, King KS. Cognitive impact of lacunar infarcts and white matter hyperintensity volume. *Dement Geriatr Cogn Dis Extra*. 2015;5:170-175.
41. Akoudad S, Wolter FJ, Viswanathan A, et al. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 2016;73(8):934-943.
42. Ning K, Zhao L, Matloff W, Sun F, Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. *Sci Rep*. 2020;10(1):10.

How to cite this article: Vintimilla R, Hall J, King K, et al. MRI biomarkers of small vessel disease and cognition: A cross-sectional study of a cognitively normal Mexican American cohort. *Alzheimer's Dement*. 2021;13:e12236. https://doi.org/10.1002/dad2.12236

APPENDIX A: STUDY GROUP COLLABORATORS

HABS-HD MPIs: Sid E O'Bryant[1], Kristine Yaffe[2], Arthur W Toga[3], Robert Rissman[4], & Leigh Johnson[1]; and the HABS-HD Investigators: Meredith Braskie[3], Kevin King[5], James R Hall[1], Melissa Petersen1, Raymond Palmer[6], Robert Barber[1], Yonggang Shi[3], Fan Zhang[1], Rajesh Nandy[1], Roderick McColl[7], David Mason1, Bradley Christian[8], Nicole Philips[1], Stephanie Large[1], and Rocky Vig[1].

[1]University of North Texas Health Science Center, Fort Worth, Texas, 76107, United States

[2]University of California San Francisco, San Francisco, California, 94121, United States

[3]University of Southern California, Los Angeles, California, 90133, United States

[4]University of California San Diego, La Jolla, California, 92093, United States

[5]Barrow Neurological Institute, Phoenix, Arizona, 85013, United States

[6]University of Texas Health Science Center at San Antonio, San Antonio, Texas, 78229, United States

[7]The University of Texas Southwestern Medical Center, Dallas, Texas, 75390, United States

[8]University of Wisconsin-Madison, Madison, Wisconsin, 53705, United States