

RESEARCH ARTICLE

Vascular risk profile and white matter hyperintensity volume among Mexican Americans and non-Hispanic Whites: The HABLE study

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Abstract

Introduction: Among vascular risk factors we hypothesized that an increased prevalence of diabetes in Hispanics would be associated with greater white matter hyperintensity (WMH) volume, which may contribute to cognitive decline.

Methods: A total of 1318 participants (60% female; 49% Hispanic, 51% non-Hispanic White; age 66.2 ± 8.9 years) underwent clinical evaluation and brain magnetic resonance imaging (MRI). WMH volume associations were assessed with age, sex, and ethnicity and then with vascular risk factors in a selective regression model.

Results: WMH volume was greater with older age ($P < .0001$), Hispanic ethnicity ($P = .02$), and female sex ($P = .049$). WMH volume was best predicted by age, diastolic blood pressure, hypertension history, hemoglobin A1c (HbA1c), white blood cell count, and hematocrit ($P < .01$ for all). Elevated HbA1c was associated with greater WMH volume among Hispanics (parameter estimate 0.08 ± 0.02 , $P < .0001$) but not non-Hispanic Whites (parameter estimate 0.02 ± 0.04 , $P = .5$).

Discussion: WMH volume was greater in Hispanics, which may be partly explained by increased WMH volume related to elevated HbA1c among Hispanics but not non-Hispanic Whites.

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KEYWORDS

cerebral microvascular disease, diabetes, Hispanic, leukoaraiosis, white matter hyperintensity

1 | BACKGROUND

Mexican Americans are diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD) at younger ages^{1,2} and with more rapid disease progression,^{1,3} and the reasons for this disparity are unknown. Some studies have suggested that Hispanics may be at higher risk for vascular contributions to dementia.⁴ The incidence and severity of diabetes are increased among Mexican Americans.² The presence of cerebral microvascular disease among individuals with diabetes is a strong predictor of cognitive decline.⁶ Diabetes and glucose intolerance have been associated with increased white matter hyperintensity (WMH) volume, a magnetic resonance imaging (MRI) marker of brain microvascular disease, in some population-based studies^{7,8} but not in others.⁹ The contribution of diabetes to accelerated brain aging and cognitive decline among Mexican Americans remains unclear.²

The Healthy Aging Brain in Latino Elders (HABLE) study was formed to identify the impact of vascular and metabolic conditions contributing to disparities in Alzheimer's disease (or AD) and mild cognitive impairment (or MCI) among Mexican Americans. In this study, we hypothesized that the presence of diabetes and glucose intolerance as indicated by elevated hemoglobin A1c (HbA1c) would be associated with increased WMH volume in Hispanics but not non-Hispanic Whites. To test this hypothesis, we aimed to quantify the associations between diabetes and other vascular risk factors that have been associated with microvascular brain insult with WMH volume and evaluate for differences between Mexican Americans and non-Hispanic Whites among the 1318 participants of the HABLE study.

2 | METHODS

The HABLE study is a community based, epidemiological study of cognitive aging among Mexican American and non-Hispanic White elders. The HABLE study uses a combination of community-based participatory research methods and targeted marketing based on zip codes for recruitment, as discussed in prior publications.^{10,11} We performed baseline evaluations for 1318 participants (60% female, 49% Hispanic, and 51% non-Hispanic White; average age 66.2 ± 8.9 years) with written informed consent. Participants underwent a clinical evaluation and 3T brain magnetic resonance imaging (MRI) on a Siemens Skyra (Siemens Healthineers AG; Erlangen, Germany). All MRI studies were obtained on the same scanner within 1 month of the clinical evaluation. All imaging was reviewed by a subspecialty trained neuroradiologist; Imaging exclusion criteria included evidence of encephalomalacia of any cause involving the cortex or over 1.5 cm in diameter evidence of brain surgery.

Participants underwent a physical examination for assessment of body mass index (BMI), and systolic and diastolic blood pressure (mm Hg) was obtained as the average across two measurements.

Clinical laboratory measures were conducted by Quest Laboratories using standard clinical procedures, with all results provided back to participants. Fasting blood samples were assayed for total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, serum glucose, estimated glomerular filtration rate, creatinine, thyroid-stimulating hormone (TSH), thyroxine (T4), vitamin B12, folate, albumin, bilirubin, alkaline phosphatase, aspartate transaminase, and alanine aminotransferase.

Designation of hyperlipidemia, diabetes, and hypertension were assigned as follows: hyperlipidemia as defined by self-report OR use of cholesterol-lowering agents OR total serum cholesterol >220 mg/dL OR LDL >140 mg/dL; diabetes mellitus as defined by self-report OR history of treatment for diabetes with insulin or oral hypoglycemic agent OR fasting glucose >126 mg/dL; hypertension as defined by self-report OR use of antihypertensive medications OR documented systolic blood pressure >140 mm Hg OR diastolic blood pressure >90 mm Hg. Participants reporting a history of diabetes were asked for age at onset, and the duration of disease was calculated.

Image analysis: WMH volume was measured from T1 Magnetization Prepared Rapid Gradient Echo (MPRAGE) and fluid-attenuated inversion recovery (FLAIR) using the Statistical Parametric Mapping (SPM) Lesion Segmentation Toolbox Lesion Growth Algorithm (www.statisticalmodelling.de/1st.html)¹² as described previously.¹³ The initial segmentation threshold was set to .3 based on visual inspection. Estimated intracranial volume (ICV) was derived from FreeSurfer v6.0 analysis of T1 MPRAGE¹⁴ (surfer.nmr.mgh.harvard.edu).

Statistical analysis was performed with JMP Pro Version 14, (SAS Institute; Cary, North Carolina, USA). Ethnicity was included as a predictor of WMH adjusted for ICV. Age and sex were included as covariates. Log [WMH (ml) +1] was used to achieve a more normal distribution. Vascular and metabolic risk factors (see Table 1) were then added as potential predictors in a best-fit linear regression model using stepwise selection minimizing Bayesian information criterion. *P*-values were adjusted for false discovery rate for multiple comparisons¹⁵ for demographics and vascular variables included as predictors, with significance at $P < .05$ using two-tailed tests. Adjusted WMH values were taken from residuals from a model with age, sex, and ICV as independent predictor variables and log (WMH +1) as the dependent variable to be predicted. Given the higher prevalence of diabetes among Hispanics versus non-Hispanic Whites in our cohort, we conducted further tests to more precisely assess ethnic difference in the association between HbA1c and WMH volume. The parameter estimates for HbA1c predicting WMH volume for non-Hispanic Whites versus Hispanic Whites were compared using an unpaired

two-tailed *t*-test. Because the relationship between HbA1c and WMH volume may be non-linear, additional analysis was then performed for clinical categories of diabetes severity based on HbA1c range. First, HbA1c was split into ordinal categories based on levels from the American Diabetes Association (ADA) guidelines with normal <5.7%, pre-diabetes $\geq 5.7\%$ but less than 6.5%, and diabetes $\geq 6.5\%$. This was used to predict adjusted WMH value, determined as described above, as the dependent outcome variable first for the entire population and then separately for Hispanics and non-Hispanic Whites. We further evaluated a four-category ordinal model for HbA1c with an additional category for poorly controlled diabetes where HbA1c >8%.

Finally, we evaluated whether the use of different diabetes-related treatments might help account for ethnic differences we observed in the association between HbA1c and WMH volume. We first evaluated insulin use, oral diabetes medication use, following a diet to reduce diabetes risk, and HbA1c as predictors of residual WMH volume using a best-fit linear regression model using stepwise selection minimizing Bayesian information criterion. The factors, if any, from this model that were significant predictors of WMH volume would then be forced into the overall best predictive model for WMH in the whole population and then stratified for Hispanic and non-Hispanic White.

3 | RESULTS

The proportion of Hispanic women ($n = 650$) was higher ($P < .0001$), with 67% female ($n = 433$) versus 54% female ($n = 357$) among non-Hispanic Whites ($n = 668$). The average age among Hispanics was lower ($P < .0001$) at 63.1 ± 8.0 years compared with 69.2 ± 8.7 years for non-Hispanic Whites, with proportion by age stratified by age and sex shown in Figure 1. The distribution of clinical variables for the whole cohort and stratified by ethnicity are shown in Table 1. Among participants with a history of diabetes, age at onset was 53.6 ± 11.3 years and duration was 12.5 ± 9.2 years. Average age at diabetes onset for Hispanics was 51.8 ± 10.7 years, which was significantly younger ($P < .0001$) than for non-Hispanic Whites at 58.4 ± 11.5 years. The duration of diabetes among Hispanics was 12.8 ± 9.4 years, which was not significantly different ($P = .8$) than the 11.6 ± 8.6 years duration for non-Hispanic Whites.

Older age (estimate 0.049 ± 0.002 , $P < .0001$), Hispanic ethnicity (estimate 0.103 ± 0.044 , $P = .0197$), and female sex (estimate 0.096 ± 0.049 , $P = .0488$) were all associated with greater WMH volume (adjusted for ICV). The best-fit model for predictors of WMH is shown in Table 2. Sex and Hispanic ethnicity were no longer significant after the inclusion of vascular risk factors. We then compared the relationship between WMH volume and risk factors by ethnic group and found that increased HbA1c, a measure of chronic hyperglycemia, was a more significant predictor of increased WMH among Hispanics than among non-Hispanic Whites (comparison of parameter estimates, $P < .0001$). Duration of diabetes and other variables shown in Table 1 that were also evaluated as predictors did not significantly contribute to best model fit in predicting WMH volume.

RESEARCH IN CONTEXT

- 1. Systematic Review:** Most prior studies evaluating vascular risk factors linked to brain microvascular disease have not included Hispanics. Hispanics have a higher prevalence of diabetes but the association of this disparity with brain vascular health is unclear. In addition, there is substantial diversity among Hispanics, and the Mexican American cohort reported here may have distinct differences from prior studies of note, such as the Northern Manhattan Study, which is predominantly Caribbean Hispanic.
- 2. Interpretation:** We have shown that diabetes among Hispanics but not non-Hispanic Whites is associated with a larger burden of white matter hyperintensity (WMH) volume, an important marker of vascular risk for dementia. This difference was not explained by ethnic differences in disease severity, treatment, or duration of onset.
- 3. Future Directions:** Further work is needed to understand the ethnic differences in the association between diabetes and WMH, which was found to be stronger for Hispanics than for non-Hispanic Whites.

Additional analysis was performed to better understand the non-linear relationships between HbA1c, WMH volume, and ethnicity using HbA1c clinical categories for diabetes severity. HbA1c evaluated as normal, pre-diabetes, and diabetes showed a significant difference in WMH volume among those in the HbA1c diabetes range versus pre-diabetes and normal ($P < .0001$) but no significant difference between normal and pre-diabetes ($P = .9$). Stratifying this predictive model by ethnicity, HbA1c categories were associated with WMH volume for Hispanics ($P < .0001$) but not for non-Hispanic Whites ($P = .3$). Differences in WMH volume by HbA1c clinical groups for the overall sample and then stratified by Hispanic ethnicity as shown in Figure 2.

Secondary analysis was then performed to probe the impact of poor glycemic control and insulin use. We hypothesized that Hispanics may have more extreme or poorly controlled diabetes that may account for the ethnic differences we observed. To evaluate this, those in the diabetes range (HbA1c ≥ 6.5) were split into good versus poor glycemic control using a cut-off of HbA1c >8; no significant difference in WMH volume ($P = .7$) was seen comparing those with poor versus appropriate glycemic control. Using this expanded HbA1c four-point ordinal scale (normal, pre-diabetes, diabetes, poorly controlled diabetes) did not alter the lack of significant associations for elevated HbA1c among non-Hispanic Whites.

4 | DISCUSSION

Our study supported our hypothesis that elevated HbA1c in the diabetes range among Hispanics is linked with increased WMH volume

TABLE 1 Distribution of clinical variables in the overall cohort and stratified by Hispanic ethnicity

	Total (n = 1318) Count, Percent	Hispanic (n = 650) Count, Percent	non-Hispanic (n = 668) Count, Percent	Hispanic versus non-Hispanic P value*
Hx Hypertension	654, 50%	335, 52%	319, 48%	<.0001
Hx High Cholesterol	685, 52%	347, 53%	338, 51%	.003
Hx Diabetes	285, 22%	209, 32%	76, 11%	<.0001
HbA1c Category				<.0001
Pre-diabetes	331, 25%	202, 31%	129, 19%	
Diabetes	235, 18%	188, 29%	47, 7%	
	Mean SD	Mean SD	Mean SD	P value*
BMI	29.8 ± 6.0	30.8 ± 5.8	28.9 ± 6.0	.0004
Systolic Pressure	136 ± 19	139 ± 21	133 ± 17	<.0001
Diastolic Pressure	81.2 ± 10.4	82.4 ± 10.8	80.0 ± 9.8	.007
Total Cholesterol	183 ± 40	185 ± 41	182 ± 40	.02
HDL Cholesterol	53.9 ± 16.3	50.3 ± 13.9	57.4 ± 17.6	<.0001
LDL Cholesterol	105 ± 33	107 ± 33	102 ± 32	.5
Triglycerides	137 ± 89	154 ± 100	120 ± 73	<.0001
Glucose	109 ± 37	117 ± 46	101 ± 24	<.0001
Hemoglobin A1c	5.98 ± 1.33	6.40 ± 1.60	5.57 ± 0.79	<.0001
Estimated GFR	80.4 ± 16.9	86.0 ± 16.5	74.9 ± 15.5	<.0001
Albumin	4.27 ± 0.26	4.26 ± 0.27	4.27 ± 0.25	.12
Bilirubin	0.58 ± 0.25	0.56 ± 0.26	0.60 ± 0.23	.6
Alkaline phosphatase	74.5 ± 23.0	80.2 ± 24.2	69.1 ± 20.3	<.0001
AST	21.0 ± 10.4	21.7 ± 12.9	20.3 ± 7.1	.02
ALT	22.0 ± 16.9	23.8 ± 19.6	20.3 ± 13.7	.016
TSH	2.24 ± 1.54	2.36 ± 1.75	2.12 ± 1.30	.0003
T4	1.19 ± 0.20	1.19 ± 0.19	1.19 ± 0.20	.99
Vitamin B12	638 ± 422	625 ± 427	650 ± 417	.10
Folate	15.8 ± 5.5	14.6 ± 5.0	17.0 ± 5.7	<.0001
White Blood Cell Count	6.38 ± 2.16	6.65 ± 2.50	6.12 ± 1.73	<.0001
Hematocrit	41.0 ± 3.8	40.7 ± 4.1	41.3 ± 3.4	.009

Note: Count and percent are reported for binary categorical variables and mean ± standard deviation (SD) is reported for continuous variables.

*P value for ethnic differences is adjusted for age and sex and incorporates multiple comparison correction using false discovery rate. HbA1c category was considered as an ordinal categorical variable.

compared with non-Hispanic Whites. Hispanics had increased WMH volume, equivalent to about 2 years of increased age compared with non-Hispanic Whites. For the entire sample, a best-fit model showed that older age, elevated HbA1c, history of hypertension, high diastolic blood pressure, increased WBC count, and decreased hematocrit were significantly related to increased WMH volume. Hispanic ethnicity was no longer associated with increased WMH volume after accounting for effects in the model from these risk factors. Identifying increased WMH volume among Hispanics related to diabetes suggests increased vascular risk for cognitive decline,⁶ which will need to be assessed as we follow this prospective cohort.

An increased association between WMH volume and HbA1c among Hispanics may indicate an increased susceptibility to vascular brain insult related to impaired glucose metabolism. The increased prevalence of impaired glucose metabolism among Hispanics would be expected to be associated with a proportionally larger volume of WMH. HbA1c for Hispanics in our study averaged $6.4 \pm 1.6\%$, which is at the upper end of the pre-diabetes range,¹⁶ whereas non-Hispanic Whites were significantly lower ($P < .0001$) at $5.6 \pm 0.8\%$, which is in the normal range. The increased prevalence of diabetes did not by itself account for the ethnic difference we observed. Each unit elevation in HbA1c was associated with more than 3 times greater WMH volume

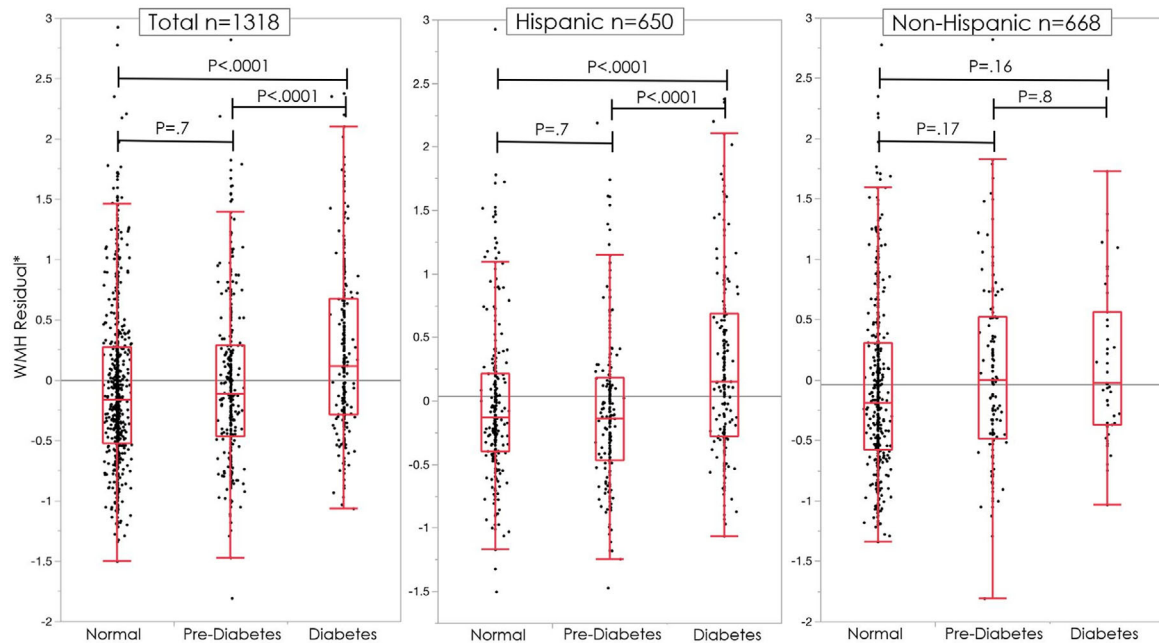


FIGURE 1 Distributions of age in years by ancestry and sex. Hispanic (purple, top row) and non-Hispanic (orange, bottom row), women (solid fill, left column), and men (dashed, right-column)

TABLE 2 Predictors of WMH Volume from a best-fit model of vascular risk factors

Term	All (n = 1318)		Hispanic n = 650		Non-Hispanic (n = 668)	
	Estimate ± SD	P value	Estimate ± SD	P value	Estimate ± SD	P value
Age	0.048 ± 0.002	<.0001	0.043 ± 0.003	<.0001	0.052 ± 0.003	<.0001
Diastolic BP	0.006 ± 0.002	.001	0.007 ± 0.002	0.01	0.006 ± 0.003	.044
Hypertension	0.105 ± 0.038	.007	0.070 ± 0.053	0.2	0.151 ± 0.057	.01
HbA1C	0.064 ± 0.014	<.0001	0.076 ± 0.016	<.0001	0.023 ± 0.035	.4
WBC	0.037 ± 0.009	<.0001	0.031 ± 0.010	0.004	0.051 ± 0.016	.004
Hematocrit	-0.021 ± 0.005	.0001	-0.018 ± 0.007	0.01	-0.026 ± 0.008	.004

Note: The model was then stratified by ethnicity to identify differences between Hispanics versus non-Hispanic Whites.

Abbreviation: Diastolic BP, Diastolic Blood Pressure; HbA1c, Hemoglobin A1c; WBC, White Blood Cell count; WMH, white matter hyperintensity.

*The following variables were also evaluated as potential predictors of WMH volume but did not contribute to model fit using Bayesian information criterion: Use of insulin, duration of diabetes, history of diabetes, serum glucose, body mass index, systolic blood pressure, total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, thyroid-stimulating hormone (TSH), thyroxine (T4), vitamin B12, folate, albumin, bilirubin, alkaline phosphatase, Aspartate transaminase (AST), and Alanine transaminase (ALT). WBC and hematocrit were imputed as the mean for two individuals with missing values.

among Hispanics compared with non-Hispanic Whites. Furthermore, the association between HbA1c and WMH volume for non-Hispanic Whites was not statistically significant. To increase confidence in this finding, we further evaluated glucose intolerance using several additional models. HbA1c was evaluated by grouping individuals into disease categories (normal, pre-diabetes, and diabetes). To assess the impact of poorly controlled diabetes we added a category for poorly controlled diabetes for those with HbA1c >8.0%, but there was still no significant association for non-Hispanic Whites.

Differences in susceptibility for brain vascular insult related to glucose intolerance may contribute to a distinct dementia risk factor pro-

file among our Mexican American Hispanic cohort.¹⁻³ In distinction to our findings related to WMH volume, our prior work in this cohort showed diabetes and elevated HbA1c to be a risk factor for dementia among non-Hispanic Whites but saw only a possible trend among Hispanics.² Part of this may be due to the younger age of Hispanics in these studies, lowering the incidence of dementia and the power to identify associated risk factors. This highlights the importance of evaluating markers of brain insult, such as WMH, to predict risk for dementia prior to onset of permanent cognitive decline.

Several other vascular factors were associated with increased WMH volume for both Hispanics and non-Hispanic Whites. Higher

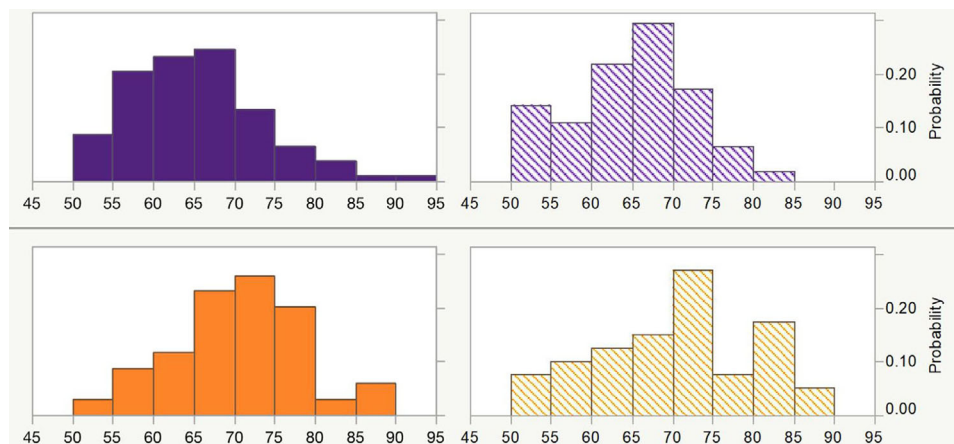


FIGURE 2 Elevated hemoglobin A1c (HbA1c) in the diabetes range, but not pre-diabetes, is associated with increased white matter hyperintensity (WMH) volume (adjusted for age, sex, and intracranial volume). Stratifying by ethnicity showed that HbA1c in the diabetes range was associated with increased WMH in Hispanics but not in non-Hispanic Whites. Comparisons between diabetes categories used Tukey's test. *Residual WMH values were obtained by adjusting the log of (WMH + 1) by age, sex, and intracranial volume

observed diastolic blood pressure or history of treated hypertension was associated with higher WMH volume. This association for diastolic blood pressure and WMH has been shown previously among Caribbean Hispanics in the Northern Manhattan Study.¹⁷ Elevated white blood cell count, associated with increased WMH, is an indication of an increased systemic inflammatory state, which has been associated with neuroinflammation and white matter injury.¹⁸ We found recently that diabetes was associated with an inflammatory proteomic profile among this HABLE cohort.¹⁹ In the present study, inflammation related to diabetes did not account for this association, as increased WBC and HbA1C were both independent predictors of increased WMH volume. Finally, reduced hematocrit was also associated with increased WMH volume. Reduced hematocrit results in a reduced oxygen carrying capacity of blood, which necessitates greater flow to maintain the same metabolic rate²⁰; this may increase susceptibility for ischemic damage.

Although we have identified associations related to Mexican American background, much of this may relate to socioeconomic status, which can be difficult to adequately capture and can have far reaching effects on health. Having now identified a difference in diabetes association with brain health among members of this cohort, we plan to focus in future work on understanding how social factors may interact with health. Some of these factors may comingle with diabetes and not be readily apparent in our current study. It is important to track longitudinal changes to understand the causal relationships as the current study can only establish cross-sectional associations. The HABLE study is currently conducting Wave 2 longitudinal assessments, so these findings will be re-examined over time in the near future.

Hispanics had increased WMH volume, equivalent to about 2 years of increased age compared with non-Hispanic Whites. Each unit elevation in HbA1c was associated with a larger elevation in WMH volume among Hispanics compared with non-Hispanic Whites. This suggests that the impact of increased diabetes prevalence among Hispan-

ics on brain health is potentiated by a heightened susceptibility to brain microvascular insult.

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CONFLICT OF INTERESTS

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