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Association of Physical Activity Levels and Brain White Matter in Older Latino Adults

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Abstract

Objective: Investigate the associations between self-reported physical activity (PA) engagement and white matter (WM) health (i.e., volume, integrity, and hyperintensities) in older Latinos. *Design:* Cross-sectional study with community-dwelling older adults from predominantly Latino neighborhoods.

Participants: Thirty-four cognitively healthy older Latinos from two different cohorts.

Measurements: Participants self-reported demographic information, PA engagement [Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults] and magnetic resonance imaging (MRI). We used high-resolution three-dimensional T1- and T2-FLAIR weighted images and diffusion tensor imaging acquired via 3T MRI. We performed a series of hierarchical linear regression models with the addition of relevant covariates to examine the associations between self-reported PA levels and WM volume,

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integrity, and hyperintensities (separately). We adjusted *p*-values with the use of the Benjamini-Hochberg's false discovery rate procedure.

Results: Higher reported levels of leisure-time moderate-to-vigorous PA were significantly associated with higher WM volume of the posterior cingulate (β = 0.220, SE = 0.125, 95% CI 0.009–0.431, $p = 0.047$) and isthmus cingulate (β = 0.212, SE = 0.110, 95% CI 0.001–0.443, $p = 0.044$) after controlling for intracranial volume. Higher levels of total PA were significantly associated with higher overall WM volume of these same regions (posterior cingulate: β = 0.220, SE = 0.125,CI 0.024–0.421, $p = 0.046$; isthmus cingulate:β = 0.220, SE = 0.125, 95% CI 0.003–0.393; $p = 0.040$). Significant *p*-values did not withstand Benjamini-Hochberg's adjustment. PA was not significantly associated with WM integrity or WM hyperintensities.

Conclusion: Higher levels of PA, particularly higher leisure-time moderate-to-vigorous PA, might be associated with greater WM volume in select white matter regions key to brain network integration for physical and cognitive functioning in older Latinos. More research is needed to further confirm these associations.

Keywords

Brain white matter; physical activity; older adults; Latinos

Introduction

Older Latinos are at higher risk of cognitive impairment due to increased prevalence of risk factors for cognitive decline such as obesity, type 2 diabetes, and metabolic syndrome [1]. From 2000 to 2012, the prevalence of cardiovascular diseases (e.g., hypertension, diabetes, heart disease, and stroke) increased in all racial/ethnic groups, but the rate of increase was highest among Latinos [2]. Epidemiological studies demonstrated that older Latinos had 1.5 times the odds of dementia compared to non-Latino whites after adjustment for modifiable and non-modifiable risk factors [2,3]. The adoption of healthy lifestyles can potentially attenuate this increased risk, with physical activity (PA) being a central behavior to healthy lifestyles. More specifically, PA is effective for reducing obesity, type 2 diabetes, and metabolic syndrome [4]; and a key modifiable factor for improved brain health [5].

PA engagement during leisure time is associated with reduced risk of Alzheimer's disease and related dementias (ADRD)[6,7], and was added by the Physical Activity Guidelines for Americans as beneficial to cognitive health and reduced dementia risk [4,8]. Leisure-time PA (LTPA) has been deemed as a promising precision prevention target for brain health [9]. There is a salient need to evaluate the relationship between LTPA and brain health, especially among populations at higher risk of developing ADRD [9]. Recently, studies have shown that an important contributor to better cognitive health in older adults is healthy brain white matter (WM)[10]. WM tracts enable the transfer of information within the brain, allowing for a rapid and efficient integration of neural systems necessary for higher order cognitive operations (e.g., memory and executive function) [10]. Thus, it follows that one of the fundamental drivers of age-related cognitive decline is the disruption of WM; disruption which also contributes to the clinical expression of ADRD [11]. In fact, the susceptibility to WM alterations within anterior (i.e., prefrontal) regions is highly associated with age [12,13],

while alterations within more posterior (i.e., parietal) regions are thought to be associated with ADRD [14].

WM disruption can be measured using several metrics including total (i.e., global) and regional volumes[15], diffusion tensor imaging (DTI)-derived WM integrity [13], and WM hyperintensities (WMH)[16]. Those WM metrics have been associated with cognitive function in healthy older adults. The most general form of measuring WM health is through global WM volume, which represents roughly half of the total brain volume [10], and has accelerated decline starting at 60 years old [17]. Another important measure of WM health relates to the presence of injuries, which are evident hyperintensities [18] or bright areas on magnetic resonance imaging (MRI) [19–21]. The presence and progression of WMH are considered an indicator of cognitive decline [22].

Alterations and subtle damage in WM can signal degeneration of the tissue. The susceptibility to steep declines in WM is particularly high among older adults, with anterior regions showing greater degradation [12,13,23]. This degeneration is captured as decreased fractional anisotropy as measured with DTI acquired via MRI. Fractional anisotropy is a measure of the directional dependence of diffusion [24], reflecting fiber density, integrity, orientation and coherence [25]. Reduced fractional anisotropy in aging has been linked to loss of axon and myelin integrity, signaling to reduced WM integrity [23]. Improving WM integrity is essential to prevent declines in cognitive performance and keep older adults physically and cognitively independent [12].

These three WM metrics (i.e., volume, hyperintensities, and integrity) provide complementary measures of WM health. Nonetheless, their relationship is yet to be fully determined. Accumulating evidence suggests that DTI measures (i.e. WM integrity) offer an assessment of pathologic changes that precede and predict the development of WMHs or WM volume loss [26–28]. These WM metrics form the basis of the neuroimaging analyses conducted in the present study. Although previous literature suggests the interconnectedness between WM metrics, this understanding goes beyond the scope of the study.

Importantly, all WM metrics mentioned have been correlated with PA in older adults. Stillman & Erickson (2018)[29] outlined a model of how PA affects brain morphology based upon the extant literature that includes each of these WM metrics. Data suggest that higher levels of overall PA are associated with higher global WM volumes [30], global WM integrity [30,31], and less WMHs [32]. Higher levels LTPA or exercise have been associated with increased global WM integrity [33,34] as well as microstructural WM integrity (i.e., DTI-derived measures thought to reflect underlying axonal and myelin health) [35]. Studies have also demonstrated an association between higher levels of PA and higher regional WM volumes. Ho and colleagues (2011)[36] found that more PA engagement was associated with greater WM volume of the corona radiata and the parietal-occipital junction, after controlling for age, sex, and education. Higher WM volumes in temporal, parietal and occipital regions were also observed in master athletes relative to sedentary older adults [37]. Taken together, the literature associating PA with WM in primarily non-Latino white populations warrants an investigation of these same WM measures in older Latinos.

Collectively, available evidence points to the association of increased PA levels (total PA and LTPA) and increased global and regional WM volume, WM integrity, and reduced WMH. However, studies investigating the association of PA and WM metrics were conducted in countries without a representative Latino population or when conducted in the U.S. did not include Latinos in the sample. Given the older Latino population demonstrates increased WMHs compared to non-Latino whites [38], longer duration of memory problems prior to obtaining a diagnosis of ADRD [39], and an increased likelihood of developing ADRD than non-Latino whites [39], studies that include older Latinos are needed. From a public health standpoint, disparities in dementia prevalence between Latinos and non-Latino whites have increased [2], which makes it necessary to have a better understanding of the associations between a pivotal health behavior (i.e., PA) to reduce risk factors for dementia and brain WM metrics (i.e., WM volume, integrity, and hyperintensities) that are associated the clinical expression of ADRD. To fill this important gap in the literature, the present study aimed to answer the following research question: are there associations between self-reported PA (i.e., LTPA of light, moderate, and moderate-to-vigorous intensities, and total PA) and global and regional WM volumes, DTI-derived WM integrity, and WMHs in older Latinos? We hypothesized that higher levels of self-reported PA (i.e., LTPA of light, moderate, and moderate-to-vigorous intensities, and total PA) would be associated with higher global and regional WM volumes, higher WM integrity, and lower WMHs.

Materials and Methods

Study Design

This secondary data analysis combined data from two cohort studies with demographically similar participants and identical neuroimaging protocols. Studies were approved by the University of Illinois at Chicago Institutional Review Board (IRB) (Protocol # 2015-0497), with additional approval by the Rush University IRB (FWA # 00000482). Each was conducted per the Declaration of Helsinki with written informed consent obtained from all participants. The first study (Study 1) was a pilot trial examining the impact of the BAILAMOS™ dance program on cognitive function, brain structure, and brain connectivity in older Latino adults. Baseline data from all participants in both intervention and control groups are included in this cross-sectional study. The second study (Study 2) was a large observational study of brain aging and cardiovascular disease risk factors [40–42]. Cross-sectional data from participants identifying as Hispanic or Latino were included in the current analysis.

Participants and Procedures

Participants of both cohorts were English and/or Spanish speaking community-dwelling older Latinos recruited via community outreach strategies (e.g., advertisements, flyers, and word of mouth) in Chicago Latino neighborhoods. Individuals included in this study were screened according to common inclusion criteria across the two studies: (a) age ≥ 60 years; (b) self-reported Latino/Hispanic; (c) cognitively healthy as measured by the Mini-Mental State Exam (MMSE) [43] (score ≥ 14 in a modified version [21-point] for telephone administration for Study 1 [44], and a score ≥ 24 on the full version for Study 2). The modified MMSE has shown a Pearson correlation of 0.968 ($p < .001$) between the

standard version and the 21-point MMSE[44]. Previous studies using the 30-point MMSE with older adults with low educational attainment identified one-third incorrect as a cut-point for impaired/poor cognition [45]; therefore, below 14 was our cut-point to exclude participants in the screening. Common exclusion criteria were: (a) stroke within the past year; and (b) contraindications for MRI, including metallic implants. Additional study-specific criteria are outlined below.

Study 1 inclusion criteria encompassed information relevant to the dance intervention that bilingual staff obtained from interested individuals via phone. Inclusion criteria were (a) ability to speak Spanish; (b) participation in less than 150 minutes/week of aerobic exercise (c) danced < two times/month over the past 12 months; (d) willingness to be randomly assigned to treatment or control group; and (e) no plans to leave the U.S. for more than two weeks. Additionally, The Exercise Assessment and Screening for You questionnaire [46] was used to detect conditions that could prevent exercise participation.

Participants deemed eligible for Study 1 were scheduled for baseline testing. Bilingual research staff conducted data collection, which lasted one to two hours. We administered testing in Spanish or English, as requested by the participant. The initial testing session included informed consent, demographic questionnaires, and self-reported PA. During consent, the staff member showed images of the MRI machine to make sure that participants understood the details about the MRI exam and agreed to participate in the study. Participants attended a second in-person session for MRI data acquisition. Participants received a $50 gift card compensation after the data collection.

Inclusion criteria specific to Study 2 encompassed information to ensure a non-demented, non-depressed community cohort study. Described in detail elsewhere [40–42], in addition to the common components described above, additional exclusion criteria consisted of (a) self-reported current or history of neurological conditions including ADRD, mild cognitive impairment, Parkinson's disease, or any other movement or seizure disorder, (b) current or past history of Axis I or II disorders (e.g., depression or bipolar disorder) or current psychotropic medication use; (c) a history of head injury or loss of consciousness; (d) a present or past substance abuse or dependence. Individuals were not eligible for this study if they underwent cognitive testing within the past year.

For purposes of this secondary data analysis, only data on self-reported PA and WM metrics obtained via MRI are being presented. Across both studies described above, self-reported PA data were collected in a first visit using the Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults [47], and MRI data acquisition occurred in a visit at the University of Illinois at Chicago Advanced Imaging Center.

Measures

Demographic information included age, sex, education, race/ethnicity, and preferred language. Self-reported PA data were acquired through the CHAMPS Physical Activity Questionnaire for Older Adults [47]. It assesses weekly frequency and duration of physical activity in four different lifestyle domains (leisure-time, household, occupational, and

transportation PA) typically undertaken by older adults. PA intensity is obtained within each domain and for all activities according to CHAMPS developers[47] based on the Compendium of Physical Activities [48]. For the purposes of the current study, we are interested in leisure-time (light, moderate, MVPA, and total LTPA) and total PA (sum of all PA domains and intensities). The Spanish version of CHAMPS has been validated and employed with older Latino adults [49].

We also collected data on weight (lb) and height (in). Those measures were then transformed (i.e., lb to kg, and in to cm) and used to calculate the body mass index (BMI = weight/height^2). BMI categories utilized were: less than 18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), and 30.0 or more (obesity).

Neuroimaging acquisition and processing

Participants of both studies underwent the same neuroimaging protocol at University of Illinois at Chicago Center for Magnetic Resonance Research. Whole-brain images were acquired on a GE MR 750 Discovery 3T scanner (General Electric Health Care, Waukesha, WI) using an 8-channel head coil. Participants were instructed to remain still in a supine position on the scanner table. We provided earplugs to improve their comfort and positioned foam pads to minimize head movement. Sequences relevant for this data analysis were high-resolution three-dimensional T1- and T2-FLAIR weighted images and diffusion MRI.

T1-weighted image acquisition employed a Brain Volume (BRAVO) sequence with the following parameters –field of view: FOV = 22mm; voxel size = 0.42×0.42×1.5mm3; 120 contiguous axial slices; TR/TE = 1200ms/5.3ms; flip angle = 13°. T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired using a two-dimensional PROPELLER sequence to improve robustness against motion (FOV=22cm, voxel size=0.35×0.35×3.0mm^3, 40 contiguous axial slices, TR/TI/TE=9500ms/2500ms/93.3ms, flip angle=142.35°). Lastly, diffusion MRI was acquired using a 2-D spin-echo EPI sequence (FOV=20mm; voxel size=0.78×0.78×3.0mm^3; TR/TE=5,525/93.5ms; flip angle=90°). Forty contiguous axial slices aligned to the AC-PC line were collected in 32 gradient directions with b=1400s/mm2 and six baseline (b0) images.

WM volumes, both global and regional, as well as total intracranial volume (ICV) were quantified using FreeSurfer 6.0 software (https://surfer.nmr.mgh.harvard.edu/) [50–53]. In addition to global WM volume combining right and left hemispheres, regional WM volumes (combining right and left hemispheres) included frontal, parietal, temporal, and occipital regions as well as the anterior, isthmus, and posterior portion of the cingulate.

DTI-derived WM integrity data were processed first by aligning each subject's raw diffusion-weighted images to their mean b0 image using the FSL eddy-correct tool to correct for head motion and eddy current distortions. The gradient table was adjusted accordingly. Non-brain tissue was removed using the Brain Extraction Tool (BET) [54] from the FSL package [55] (http://fsl.fmrib.ox.ac.uk/fsl). We used Tract-Based Spatial Statistics (TBSS) [56] to quantify the WM diffusion measure of fractional anisotropy. Then fractional anisotropy was extracted and estimated on each voxel using *dtifit* from the FSL package.

In order to extract WMH data, T1- and T2-FLAIR images were pre-processed with brain extraction (using BET [54]), and with intra-subject co-registration from FLAIR to T1 space (using FLIRT [56]) and from T1 to MNI152 standard space (using FNIRT [57]). Ten participants were manually segmented in FLAIR space as a training set. BIANCA (Brain Intensity AbNormality Classification Algorithm, part of FSL), a fully automated and supervised method for WMH detection, was then utilized for the remaining participants as well as for the manually segmented participants [58]. The following BIANCA default options were applied: no border (excluded voxels close to the lesion's edge), number of training points for WMH (i.e., 2000), and non-WMH (i.e., 10,000). The output images were post-processed, binarized for a WMH probability map with a threshold at 0.9, and masked to exclude image artifacts. Manual editing of the WMH mask was performed as needed. Finally, the WMH volume was extracted using a minimum cluster size of 20.

Statistical analysis

Analyses were conducted in RStudio version 1.2.1335 and FSL. Descriptive data are presented as mean, standard deviation, relative, and absolute frequency. Normal distribution was inspected with histograms and Kolmogorov-Smirnov test. We log-transformed WMH volume as it did not present normal distribution. All data (self-reported PA, select WM metrics, and covariates) were then transformed into z-scores. We winsorized outliers (self-reported PA and select WM metrics) outside the Q1−1.5*IQR and Q3+1.5*IQR limits replacing those observations outside the lower limit with the value of the 5th percentile and those above the upper limit, with the value of 95th percentile.

We performed multiple linear regression models to examine the association between self-reported PA levels (i.e., light LTPA, moderate LTPA, moderate-to-vigorous LTPA, total LTPA, and total PA) and select WM metrics (i.e., volumes and hyperintensities) separately. Initial models were adjusted for intracranial volume (ICV) only (Model 1), then we hierarchically added covariates including age, sex, years of education, and BMI for the fully adjusted Model 5 unless otherwise noted. Models were performed utilizing the *lm* function in RStudio version 1.2.1335. Significance levels were set at $p < 0.05$. To account for multiple testing, we adjusted *p*-values with the use of the Benjamini-Hochberg's false discovery rate (FDR) procedure [59]. Decisions on statistically significant results were taken based on *p*-values along with confidence intervals. The analysis for WM integrity as measured by DTI-derived FA, was conducted utilizing the randomize tool on the FSL package. The initial model was adjusted for the ratio of WMH to ICV only (Model 1), we then hierarchically added the following covariates: age, sex, years of education, and BMI in the fully adjusted Model 5 (unless otherwise noted). The statistically significant threshold was set at 95%.

Results

Demographics and descriptive data

Participants (N=34) were 66.6 ± 6.4 years old, 56% female, on average, overweight (BMI 28.2±4.2 kg/m2), considered Spanish as their preferred language (88.2%), spent an average of 10 years in school, and were cognitively healthy (21-point MMSE for telephone

administration = 19.59 ± 1.56; 30-point MMSE full-version = 28.42 ± 1.24). Participants self-reported high levels of total LTPA, exceeding the 2018 Physical Activity Guidelines minimum recommendations of 150min/week of MVPA (Table 1).

Associations between self-reported physical activity and overall WM volume

Global WM volumes—Regression models showed that higher self-reported levels of PA (i.e., light LTPA, moderate LTPA, moderate-to-vigorous LTPA, total LTPA, and total PA) were not significantly associated with higher global WM volume, regardless of adjustments (data not shown).

Regional WM volumes—Higher *leisure-time MVPA* was significantly associated with higher WM volume of the posterior cingulate regardless of adjustments (Model 1: F[2,31] = 24.211, p = 0.047, β = 0.220, SE = 0.125, 95% CI 0.009–0.431, p= 0.047; fully adjusted Model 5: F[6,27]=7.932, p < 0.001, β = 0.300, SE = 0.150, 95% CI 0.008–0.609, p = 0.042. The final fully-adjusted Model 5 explained an additional 2.2% of the variance in posterior cingulate WM volume compared to Model 1 (61.6% vs. 63.4%), which did not explained significantly more variance in WMV compared to Model 1 (F[(4]=0.403, p = 0.805) (Table 2). Thus, Model 1 (with only leisure MVPA and ICV) was more parsimonious. Even though the 95% CIs did not include 0, the associations (Models 1 and 5) did not withstand FDR corrected p-value thresholding.

Likewise, we observed that higher *total PA* was significantly associated with higher WM volume in the posterior cingulate, regardless of adjustments (Model 1: F[2,31] = 25.492, p < 0.001, β = 0.220, SE = 0.125, 95% CI 0.024–0.421, p = 0.046; Model 5: F[6,27] = 8.044, p < 0.001, β = 0.289, SE = 0.140, 95% CI 0.002–0.576, p = 0.048). The fully-adjusted Model 5 explained an additional 1.9% of the variance in WM volume in the posterior cingulate compared to Model 1 (64.1% vs. 62.2%) (Table 3). The additional 1.9% did not explain significantly more variance in WMV compared to Model 1 (F[(4]=0.365, p = 0.831). Therefore, Model 1 (with only total PA and ICV) was more parsimonious. Even though the 95% CIs did not include 0, the significant associations (Models 1 and 5) did not withstand FDR corrected p-value thresholding.

Higher *leisure-time MVPA* as well as higher *total PA* were each significantly and separately associated with higher WM volume in the isthmus of the cingulate after controlling for ICV (leisure-time MVPA Model 1: F[2,31] = 32.732, p < 0.001, β = 0.212, SE = 0.110 95% CI 0.001–0.443, p = 0.044; total PA Model 1: F[2,31] = 32.879, p < 0.001, β = 0.220, SE = 0.125, 95% CI 0.003–0.393; p = 0.040). However, neither predictor withstood additional adjustments in Models 5 (all *p-values* > 0.05). Even though the 95% Cis in Model 1 did not include 0, the associations did not withstand FDR corrected p-value thresholding. Regression models showed that self-reported levels of other LTPA intensities (i.e., light, moderate, and total) were not significantly associated with regional WM volumes, regardless of adjustments.

Associations between self-reported physical activity, WMH, and WM integrity —We did not observe significant associations between self-reported PA levels and WMH or DTI-derived FA, regardless of adjustments (data not shown).

Discussion

This study aimed to investigate the associations between self-reported PA and WM volume, integrity, and hyperintensities in older Latinos. The sample self-reported high levels of engagement in PA, meeting the 2018 Physical Activity Guidelines of 150min/week. This concurs with the largest population-based study with Latinos, the Hispanic Community Health Study/Study of Latinos, which also demonstrated high engagement in MVPA among middle-aged and older adults using self-report measures [60]. Our results also suggested that higher levels of MVPA and total PA in older Latinos was associated with gross volumetrics in key regions of the cingulate - a WM structure that is critical to brain network integration for physical and cognitive functioning – with the most robust findings for the posterior cingulate.

Our results contribute to the literature in several ways. First, the association between PA and WM volume extends Sexton and colleagues' (2016) [61] systematic review and Gu et al. (2020) [9] cross-sectional study findings on the associations of higher PA and LTPA engagement and increased global WM volume, respectively. Our null result on global WM volume diverges from Sexton and colleagues and Gu and colleagues studies, but concurs with a recent cross-sectional study with 1,715 healthy middle-aged and older adults [62]. Vergoossen and colleagues demonstrated that the associations between device-assessed PA and global WM volumes did not remain significant after adjustment for demographics (e.g., age, sex, educational attainment, and BMI) and cardiovascular risk factors.

Second, our study extends Sexton and colleagues' (2016) [61] and Gu and colleagues' (2020) [9] findings to specific regional WM volumes, i.e., those within the cingulate that showed significant associations with higher moderate-to-vigorous LTPA and total PA. These regional associations suggest that higher levels of PA are associated with brain regions that play a central role in brain network integration for not only physical, but also cognitive functioning. For example, the cingulate (or cingulum bundle) is a prominent WM tract interconnecting frontal, parietal, and medial temporal brain regions commonly associated with emotional control, executive function, and memory [63]. Moreover, the cingulum bundle is affected both by normal aging [64], and by several neurological conditions, including mild cognitive impairment and ADRD [63]. Thus, our findings that higher MVPA and total PA were associated with higher WM volumes within two cingulate regions further contributes to the literature by providing an empirical foundation for longitudinal study of the potential impact of PA in older adults on the WM health of these regions. This is of special importance for older Latinos, who are at increased risk for developing ADRD [39]. Our findings may indicate that increasing PA is a potential prevention strategy for preservation of WM volume in important brain regions for cognitive health, which is major factor for quality of life in older adults and contributes greatly to late-life functioning and independence [65,66]. Furthermore, promoting engagement of older Latinos in PA might help offset the greater prevalence of risk factors for cognitive impairment in this population segment.

Of note, the statistically significant associations mentioned above did not withstand FDR corrected p-value thresholding; however, the reliance on *p*-values as a single decision criterion to indicate whether an association or effect exists or not is a matter of great debate.

[67–69] It is for this reason that we used *p*-values as well as confidence intervals to guide how we discussed our findings. And we highlight the limitations that should be considered when interpreting our results below, including the small sample size. Even though, there is a signal for potential associations between higher levels of leisure MVPA and total PA with higher WM volumes in the posterior and isthmus of the cingulate. Those are likely not entirely spurious; however, this small signal should be seen as a first step suggesting the need for more research on the relationship between PA and WM in a larger sample of older Latinos.

While beyond the scope of this cross-sectional study, the mechanisms for the positive association between moderate-to-vigorous LTPA and total PA with WM volume need to be further clarified and likely involves multiple biological mechanisms [9]. Two main hypothesized mechanisms of action to explain the benefits of higher levels of PA on higher WM structural volumes may be found in the vascular and neurobiological literature. For example, the vascular hypothesis attributes the benefits of PA for brain health to positive effects on vascular risk factors including lowered blood pressure, serum cholesterol, and BMI [70]. This, in turn, reduces the negative downstream effects on the brain typically associated with these vascular risk factors and instead ensures adequate perfusion of oxygenated blood to the brain, for example. In contrast, the neurobiological mechanism of action is hypothesized to center upon the fact that higher PA leads to exercise-induced cellular effects that promote the development not only of new blood vessels in the brain, but also new neurons (angiogenesis and neurogenesis, respectively), consequently boosting brain and, more specific to the focus of our study, WM health [71].

We did not find an association between self-reported LTPA and WM integrity, as measured by DTI-derived FA. Previous studies with healthy older adults have yielded equivocal findings. Gons and colleagues (2013) [35] found that being more physically active was associated with other DTI-derived measures of WM microstructure but not FA. Similarly, Tian and colleagues (2014) [72] classified healthy older adults into sedentary, lifestyle active, and exercise active groups. They found no difference in FA across superior longitudinal fasciculus, cingulate cortex, medial temporal lobe, and uncinate fasciculus when comparing the three groups. Another study found that higher levels of PA was associated with higher global FA, but this association became non-significant after the inclusion of covariates in the model [30]. Wolf and colleagues (2020) [73] echoed the null associations between PA (device-assessed) and DTI-derived fractional anisotropy and medial diffusivity. However, they found an interaction of widespread medial diffusivity and PA, suggesting the associations are age-dependent and global. Thus, more work may be needed to investigate alternative methods for understanding WM integrity; this remains an ongoing investigation within our group.

Another measure of WM health that was not associated with PA in our study was WMHs, much like other cross-sectional studies with healthy older adults [32,36,37,72]. Additionally, longitudinal studies found that changes in PA were not associated with decreased WMH progression over three years [74], and five years of follow-up [75]. On the other hand, however, and speaking to the divergent nature of the literature on this topic, other studies highlight a significant relationship between PA and WMH. For example, Burzynska and colleagues [32] demonstrated that higher self-reported MVPA was associated with lower WMH volume, regardless of age, gender, and cardio-respiratory fitness. Gow and colleagues [30] also found

the self-reported PA at baseline was correlated with less WMH three years later. Similar results demonstrated that current PA levels significantly predicted lower WMH volumes [34]. It is important to note that participants in these studies were older and had higher educational attainment compared to participants in our study. Therefore, our sample might be too young to have accrued as much damage to the WM, and consequently demonstrate a detectable pattern of associations between PA levels and WMH. Also, higher educational attainment might reflect important differences in cognitive reserve, which may impact WM structure and health. For example, among healthy older adults with low educational attainment, more severe WMHs were associated with poorer cognitive function, but the association was not significant among those with higher educational attainment [76].

Despite some novel findings, this study has several limitations. First, our small sample size might have prevented us from detecting more robust statistically significant associations. Second, the fact we had a small sample size and conducted several linear regression models inflated the probability of type I error. We addressed this issue by reporting *p*-values adjusted to multiple comparisons and employing 95% confidence intervals to make decisions on statistically significant findings. Third, crude models without further adjustments to confounders were more parsimonious than fully-adjusted models, suggesting that our adjustments weaken the original associations (PA and WM metrics). Perhaps because the select covariables explain a considerable degree of the variability in WM metrics in our small sample. Fourth, we relied on self-reported PA measurement, which is subject to recall bias, overestimation of PA engagement, and social desirability bias. Fifth, while we controlled for several potential confounding factors within our models, variables such as cardiovascular aspects, APOE ε4 carrier, diet, and sleep were not collected and could be considered as further confounders. Sixth, we cannot imply any causal effects due to the cross-sectional design. Lastly, while Studies 1 and 2, when considered individually, had distinct primary objectives and specific inclusion criteria (e.g., Study 1 did not screen for psychiatric illness) any potential differences between cohort participants were most likely kept to a minimum because of similar recruitment efforts and inclusion criteria.

Our study had important strengths. We focused entirely on older Latino adults, the fastest-growing minority group among older adults in the US, and a segment of the population that presents greater risk factors for cognitive decline compared to non-Latino Whites. Also, our measures of WM health spanned from gross morphometry to regional alterations in volumes, integrity, and damage. Importantly, concurring with Gu and colleagues' (2020) [9] recommendations, for those individuals at higher risk of developing ADRD it is essential to identify potential protective factors and behaviors (e.g., PA) that can slow down cognitive impairment and the trajectory into the clinical stages of ADRD. With that, policies aiming to promote PA for middle-aged and older Latinos can be advocated by researchers, community leaders, and representatives. Future studies should further investigate WM health combined with device-assessed PA in larger samples of older Latinos as well as select a set of pre-planned models to confirm the observed associations and to increase statistical power.

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Table 1.

Means and standard deviations of self-reported physical activity, white matter volume, and white matter hyperintensities volume.

Variables	*M*	*SD*
	(n = 34)	
Self-reported Physical Activity (min/week)		
Light	529.85	266.18
Leisure light	318.97	233.91
Moderate	246.62	236.23
Leisure moderate	199.41	211.51
Moderate-to-vigorous	336.62	334.84
Leisure moderate-to-vigorous	289.41	309.04
Total	866.47	517.49
Leisure total	608.38	458.08
MMSE		
Telephone administration (21-point)[a]	19.59	1.56
Full-version (30-point)[b]	28.42	1.24
White Matter Volumes (mm^3)		
Global	408261.61	54684.44
Frontal	127842.60	16867.85
Temporal	37674.27	5595.22
Parietal	67452.72	8843.20
Occipital	40970.84	5881.47
Anterior cingulate	9361.52	1255.75
Posterior cingulate	8146.20	1012.82
Isthmus of the cingulate	6652.85	882.63
White Matter Hyperintensities (mm^3)	1932.20	1085.36

[a] n = 22

[b] n = 12

Table 2.

Regression of leisure-time moderate-to-vigorous physical activity on white matter volume in the posterior cingulate.

	Dependent variable:	
	Posterior Cingulate WMV	
	Model 1	**Model 5**
Constant	0.008	−0.012
	(0.110)	(0.210)
Leisure MVPA	0.220*	0.300*
	(0.125)	(0.150)
ICV	0.758****	0.774****
	(0.111)	(0.160)
Age		0.061
		(0.152)
Sex (Female)		0.041
		(0.317)
Years of education		−0.120
		(0.127)
BMI		−0.043
		(0.129)
Observations	34	34
R^2	0.616	0.638
Adjusted R^2	0.592	0.558
Residual Std. Error	0.639 (df = 31)	0.665 (df = 27)
F Statistic	24.911**** (df = 2; 31)	7.932**** (df = 6; 27)

Note:

*p < .05

**p < .01

***p < .001

Table 3.

Regression of total physical activity on white matter volume in the posterior cingulate.

	Dependent variable	
	Posterior Cingulate WMV	
	Model 1	**Model 5**
Constant	0.005	−0.036
	(0.109)	(0.211)
Total PA	0.223*	0.289**
	(0.117)	(0.140)
ICV	0.771****	0.802****
	(0.111)	(0.163)
Age		0.062
		(0.151)
Sex (Female)		0.076
		(0.319)
Years of education		−0.110
		(0.125)
BMI		−0.040
		(0.129)
Observations	34	34
R^2	0.622	0.641
Adjusted R^2	0.597	0.562
Residual Std. Error	0.634 (df = 31)	0.662 (df = 27)
F Statistic	25.492**** (df = 2; 31)	8.044**** (df = 6; 27)

Note:

*p < .05

**p < .01

***p < .001