Research Article

Greater accelerometer-measured physical activity is associated with better cognition and cerebrovascular health in older adults

Katherine J. Bangen[1,2] , Amanda T. Calcetas[2], Kelsey R. Thomas[1,2], Christina Wierenga[1,2] , Christine N. Smith[1,2,3], Maria Bordyug[2], Einat K. Brenner[2] , David Wing[4], Conan Chen[5], Thomas T. Liu[5] and Zvinka Z. Zlatar[2]

[1]Research Service, VA San Diego Healthcare System, San Diego, CA, USA, [2]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA, [3]Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA, USA, [4]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA and [5]Center for Functional MRI and Department of Radiology, University of California, San Diego, La Jolla, CA, USA

Abstract

Objectives: Physical activity (PA) may help maintain brain structure and function in aging. Since the intensity of PA needed to effect cognition and cerebrovascular health remains unknown, we examined associations between PA and cognition, regional white matter hyperintensities (WMH), and regional cerebral blood flow (CBF) in older adults. **Method:** Forty-three older adults without cognitive impairment underwent magnetic resonance imaging (MRI) and comprehensive neuropsychological assessment. Waist-worn accelerometers objectively measured PA for approximately one week. **Results:** Higher time spent in moderate to vigorous PA (MVPA) was uniquely associated with better memory and executive functioning after adjusting for all light PA. Higher MVPA was also uniquely associated with lower frontal WMH volume although the finding was no longer significant after additionally adjusting for age and accelerometer wear time. MVPA was not associated with CBF. Higher time spent in all light PA was uniquely associated with higher CBF but not with cognitive performance or WMH volume. **Conclusions:** Engaging in PA may be beneficial for cerebrovascular health, and MVPA in particular may help preserve memory and executive function in otherwise cognitively healthy older adults. There may be differential effects of engaging in lighter PA and MVPA on MRI markers of cerebrovascular health although this needs to be confirmed in future studies with larger samples. Future randomized controlled trials that increase PA are needed to elucidate cause-effect associations between PA and cerebrovascular health.

Keywords: cerebral blood flow; white matter hyperintensities; cognition; aging; exercise; perfusion; mobile health; digital health

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Introduction

The aging population in the United States is predicted to more than double by the year 2050 (Vincent & Velkoff, 2010). This unprecedented growth will result in increased numbers of individuals living with Alzheimer's disease (AD) and related dementias (ADRD). Compared to 2020, it is projected that the number of people aged 65 and older diagnosed with AD will increase by 22% by the year 2025 ("2020 Alzheimer's Disease Facts and Figures," 2020). Research suggests that approximately 30% of AD cases can be prevented by modifiable behaviors (Livingston et al., 2020), with 21% of AD cases in the US being linked to physical inactivity (Barnes & Yaffe, 2011). In recent decades, physical activity (PA) has been consistently found to bolster cognitive abilities in healthy older adults (Ahlskog et al., 2011; Beckett et al., 2015; Colcombe et al., 2006; Domingos et al., 2021; Haeger et al., 2019; Spartano et al., 2019; Voelcker-Rehage et al., 2011; Zlatar, Godbole, et al., 2019). Supervised intervention studies have shown that PA targeting 60–80% of maximum heart rate are most favorable in changing cognitive performance, brain structure, and brain function (Colcombe et al., 2004; Sanders et al., 2019; Vidoni et al., 2015). A study involving older participants without dementia found that moderate intensity aerobic exercise can increase hippocampal volume by 2% and improve memory function (Erickson et al., 2011). Furthermore, a 3-month intervention consisting of 30-min aerobic exercise intervals three times per week, with a target heart rate starting at 65% of maximum heart rate and increasing by 5% every week, induced neurovascular plasticity among older adults (Maass et al., 2015). These findings suggest that changes in moderate to vigorous intensity physical activity (MVPA) may be necessary to affect cognitive health (Zlatar, Godbole, et al., 2019).

Despite the abundance of literature that supports the benefits of PA on brain structure, function, and cognition in aging, the mechanisms by which PA may preserve cerebrovascular health remain understudied. Both cerebral blood flow (CBF) and white matter hyperintensity (WMH) volume are indicators of cerebrovascular health that have rarely been studied together as a function of accelerometer-measured PA. Zlatar, Hays, et al., (2019) previously showed that accelerometer-measured light PA and MVPA are associated with

greater CBF in the frontal lobe of older adults with normal cognition, whereas sedentary time had an inverse association with CBF (Zlatar, Hays, et al., 2019). Similarly, a small intervention study with healthy, sedentary older men demonstrated that aerobic exercise training improves CBF by 27% in the frontal lobe (Kleinloog et al., 2019), while fitness has been associated with CBF in cognitively healthy adults at risk for AD (Dougherty et al., 2020). As such, increased CBF through long-term exercise training may be a mechanism to improve cognitive functioning (Joris et al., 2018).

WMH are frequently observed on T2 FLAIR magnetic resonance imaging (MRI) in older adults and are considered an indicator of small vessel cerebrovascular disease. It is well established that greater WMH reflects an increased risk of developing ADRD (Bangen et al., 2018, 2020; Brickman et al., 2012, 2015; Lee et al., 2016). Systematic reviews have explored associations between WMH and PA in cross-sectional and longitudinal studies, but results have been mixed (Sexton et al., 2016; Torres et al., 2015). One study, which involved 10 masters athletes and 10 sedentary older adults matched in age and education, showed that masters athletes showed an 83% reduction in deep WMH compared to their sedentary counterparts. In addition, they found an inverse relationship between deep WMH volume and life-long aerobic exercise (Tseng et al., 2013). Higher sedentary time was also associated with greater WMH in those with lower levels of kidney function (Bronas et al., 2019). Another study, however, did not find significant associations between WMH and PA in healthy older adults with memory complaints. The study did find that those who reduced their PA level over 3 years had a trend towards increased WMH (Moon et al., 2018). Different findings may be attributable to methodological differences, such as the PA assessment method used (i.e., self-report (Best et al., 2017) versus objective measures (Arnardottir et al., 2016)) and the time frame under consideration (PA for the past week, year, lifelong, etc.). Studies that measure PA objectively can provide a more accurate assessment of PA that is free of recall bias.

This study aimed to advance the literature on PA prescriptions to promote brain health by investigating if accelerometer-measured PA is associated with cognitive performance and markers of cerebrovascular health (WMH and CBF) in a sample of cognitively healthy, community-dwelling older adults. We examined the associations of continuous measures of two intensities of PA (all light PA and MVPA) with cognitive and brain health variables to help eludicate whether MVPA is necessary to observe an association with cognition and brain markers or whether lighter PA is similarly associated with these variables. We examined WMH and CBF in frontal and temporal regions, which have been implicated in cerebrovascular dysfunction in aging and dementia risk (Bangen et al., 2018; Yew et al., 2017). We examined executive functioning and memory performance, which are subserved by frontal and temporal regions, respectively. We hypothesized that higher MVPA would be associated with better cognition, lower WMH volume, and higher CBF, and would have stronger associations with these variables than less intense PA (i.e., all light PA), given evidence that moderate levels of PA may be necessary to influence brain health (Chapman et al., 2013; Hayes et al., 2013).

Method

Participants

Participants were 43 community-dwelling, English-speaking older adults. Participants were recruited from ongoing studies at the University of California San Diego's WISE lab and Shiley-Marcos Alzheimer's Disease Research Center, from ResearchMatch (https://www.researchmatch.org), flyers, community engagement talks, and by word of mouth. Participants were included if they were aged 65+, had no contraindications for MRI, were able to walk independently, had no mild cognitive impairment or dementia based on standard neuropsychological testing (Jak et al., 2009), had no history of head injury with loss of consciousness within the past 6 months or moderate-severe head injury in the past, had no major neurologic or psychiatric disorders, had no history of major vascular events, had no diabetes, had no poorly controlled medical conditions, and had no history of falls in the past year resulting in hospitalization. All participants provided written informed consent. The University of California San Diego's Institutional Review Board approved the protocols. Data included in this manuscript was obtained in compliance with the Helsinki Declaration.

Procedure

All participants were pre-screened via telephone to ensure they met study criteria. This included administration of the modified Telephone Interview for Cognitive Status (m-TICS) as a first pass screening of cognitive impairment. Those with m-TICS scores ≤34 were disqualified from further participation (Cook et al., 2009). For those who met basic criteria, an Actigraph accelerometer was mailed to measure PA, and participants were instructed to wear it for 7 days, during waking hours, in their natural environments. After the measurement period, participants brought the accelerometer to their in-person appointment, at which time neuropsychological testing was administered. If participants met our cognitive criteria (no more than two scores <1 standard deviation from age-appropriate norms within one or more cognitive domains (Jak et al., 2009)) they were scheduled for a brain MRI appointment within 1 week.

Physical activity measurement

PA was objectively measured using tri-axial accelerometers (GT3X + and GT3X-BT, ActiGraph, LLC, Pensacola, FL). Consistent with recent studies (Dohrn et al., 2018; Kerr et al., 2018), participants were instructed not to change their regular activities and to wear the accelerometer on a belt on their hip, during waking hours only, for a minimum of 12 hours per day for 1 week. To ensure compliance, all participants received two phone calls from study staff (on days 2 and 5 of the monitoring period). Participant data were considered valid at the day level only if they attained a minimum of 600 minutes of wear, consistent with National Health and Nutrition Examination Survey (NHANES) best practices (Troiano et al., 2008). Participants were included only if they wore the device a minimum of 3,000 total minutes spread across at least 4 valid days (Hart et al., 2011; Jerome et al., 2009; Trost et al., 2005). Data were processed using the ActiLife version 6 software (Pensacola, FL). The unit of measurement for accelerometers is counts per minute (CPM), with higher counts indicating greater intensity of movement. Non-wear time was determined using a modified Choi algorithm (Choi et al., 2011) in which 90 consecutive minutes of 0 counts with a 2-minute spike tolerance was screened as non-wear. Data were aggregated to 60-second epochs so published cut points could be applied. Consistent with standard practice, sedentary time was defined as time spent at < 100 CPM, all light PA as 100-1951 CPM, and MVPA as ≥ 1952 CPM (Copeland & Esliger, 2009). For the PA variables used in analyses, minutes within each intensity

level were averaged across days worn, reflecting the average time in minutes per day spent at each intensity level.

Participants were instructed to wear accelerometers during waking hours only. If sleep was observed (i.e., >20-hour wear periods) data were visually inspected to ensure that behavior was indicative of sleep (i.e., short periods of small amounts of movement consistently through the night with only very brief periods of larger amounts of movement). Data were removed using a method developed by Full et al., (2018) that involves looking for the last period of substantial movement to establish go-to-bed time, and the first period of moderate amounts of movement to establish wake up time and removing the time in between from consideration (i.e., it was converted to "non-wear" time) (Full et al., 2018).

Cognitive assessment

Participants completed the Mattis Dementia Rating Scale (DRS), the NIH Toolbox Cognition Battery (Casaletto et al., 2015), Rey Auditory Verbal Learning Test (RAVLT), the Golden Stroop Color Word Interference Test, the Wechsler Memory Scale-Revised (WMS-R) Logical Memory I and II, Trail Making test Parts A and B, and verbal fluency tests (FAS and animals). To ensure participants included in the study were cognitively unimpaired, we applied the comprehensive mild cognitive impairment (MCI) diagnostic criteria proposed by Jak et al., (2009), which requires at least two impaired test scores (>1 SD below normative means) within a cognitive domain. These diagnostic criteria are more strongly related to AD biomarkers and have greater diagnostic stability than typical diagnostic criteria requiring impaired performance on one cognitive test (>1.5 SD) (Wong et al., 2019). Individuals classified as MCI were excluded from this study (Jak et al., 2009). Normative scores were derived from the respective testing manuals and available published norms (Heaton et al., 2004; Ivnik et al., 1996).

Since executive and episodic memory performance scores are most responsive to exercise in intervention trials (Kennedy et al., 2016), we created executive and memory composite scores by converting raw scores into z-scores based on the entire sample, and then averaging across z-scores for the following tests: Executive Composite Score = Trail Making Test Part B minus Trail Making Test Part A (scores were reversed prior to averaging to reflect higher scores=better performance), Stroop Color Word Trial, and verbal fluency FAS. Note that for the Trail Making Test, a difference score (B-A) was used because it may reflect a purer measure of the executive functions required to complete Part B by subtracting sequencing, visual scanning, and psychomotor components common to both Parts A and B (R. K. Heaton et al., 1985). Memory Composite Score = WMS-R Logical Memory I and II, RAVLT Trials 1-5, RAVLT Trial 6 (short delay free recall) and RAVLT delayed recall. The executive and memory composite scores were used as cognitive outcomes in analyses.

Brain image acquisition

Imaging data was acquired on a GE Discovery MR 750 3T whole body system with a body transmit coil and an 8-channel receive-only head coil at the University of California, San Diego's Center for Functional MRI. The structural brain sequence consisted of (1) a high-resolution T1-weighted Fast Spoiled Gradient Recall (3DFSPGR) scan for anatomy and registration purposes: 172 1mm contiguous sagittal slices, field of view (FOV) = 25 cm, repetition time (TR) = 8 ms, echo time (TE) = 3.1 ms, flip angle = 12, inversion time (TI)=600 ms, 256 × 192 matrix,

Bandwidth = 31.25 kHz, frequency direction = S-I, NEX = 1, scan time = 8 min and 13 s and (2) a T2-weighted fluid attenuated inversion recovery (FLAIR) scan to detect WMH: 36 axial slices with no interslice gap at a voxel size of .47×.47 × 4.00 mm^3, FOV = 24 cm, TR = 8650 ms, TE = 136 ms, flip angle = 111, TI=2250 ms, 256 × 256 matrix, Bandwidth = 31.25 kHz, frequency direction = A/P, NEX = 1, scan time = 6 min and 40 s. CBF was quantified with a 2D Pseudo Continuous Arterial Spin Labeling (ASL) MRI (2DPCASL) sequence; TR = 4500 ms, TE = 3.2 ms, FOV = 24 cm, labeling duration = 1800 ms, post-labeling delay = 2000 ms, with a single shot spiral acquisition and a total scan time of 4:30 min plus a 40.5 s calibration scan. The calibration scan was acquired immediately after the ASL scan using a spiral readout with TR = 4.5 s and TE = 3.2 ms with 8 dummy radiofrequency (RF) pulses (amplitude set to zero) to generate a 36 s delay followed by a 90-degree RF pulse in the last repetition interval to generate proton density-weighted contrast. Field map scans were collected for off-line field map correction for signal bunching and dropouts in the frontal/medial temporal lobes.

Brain image processing

T1-weighted anatomical images

T1-weighted anatomical images were processed using FreeSurfer 6.0 software. Briefly, images underwent skull stripping, B1 bias field correction, gray matter-white matter segmentation, reconstruction of cortical surface models, and parcellation and labeling of regions on the cortical surface as well as segmentation and labeling of subcortical structures (Dale et al., 1999; Fischl et al., 2002). FreeSurfer was used to generate intracranial volume and anatomical regions of interest (ROIs) for the CBF data.

T2-weighted FLAIR images

Methods for processing the T2-weighted FLAIR images were similar to those previously described (Hoagey et al., 2021). White matter hyperintense voxels were identified on T2-weighted FLAIR images. Lesions were segmented using the lesion prediction algorithm (LPA) (Schmidt, 2017) as implemented in the lesion segmentation toolbox (LST) version 2.0.5 (www.statisticalmodelling. de/lst.html) for SPM12. This algorithm consists of a binary classifier in the form of a logistic regression model trained on the data of 53 individuals with multiple sclerosis who had severe lesion patterns. Covariates in the model include a lesion belief map as well as a spatial covariate considering voxel specific changes in lesion probability. Parameters of this model fit are used to segment lesions in new images producing a lesion probability map wherein each voxel value represents an estimated probability that it is a white matter lesion.

For quality assurance purposes, trained raters visually inspected each participant's lesion probability map overlaid on the participant's T2-weighted FLAIR image to ensure that the LST output optimally minimized false positive voxels (e.g., motion artifacts) and false negative voxels (i.e., voxels appearing as legitimate white matter lesions on the FLAIR image that were labeled as 0 in the lesion probability map). To eliminate false positive voxels in regions where white matter lesions are not biologically plausible, multiple regions of avoidance were created and combined to form an exclusion mask. To remove false positive voxels in the choroid plexus of the ventricles, the CSF probability map obtained from processing each participant's T1-weighted scan using FMRIB's Automated Segmentation Tool (FAST) (Zhang 2001) was

registered to their native FLAIR space using Advanced Normalization Tools (ANTs) (Avants 2014). The CSF probability maps in each participant's FLAIR space were thresholded at 0.5 and then binarized to obtain the CSF exclusion mask. Three additional regions of avoidance were derived on the Montreal Neurological Institute (MNI) 1mm space brain and then registered to each participant's native FLAIR space using ANTs. The regions were (1) a 2mm mid-sagittal exclusion mask to remove false positive voxels in the septum pellucidum, (2) a ventral exclusion mask (below z = 34) to eliminate false positive voxels from the cerebellum and brainstem, and (3) a dorsal exclusion mask (above z = 130) to remove false positive voxels from exiting blood vessels. The four exclusion masks were summed to create one total exclusion mask and then applied to each participant's thresholded lesion probability map.

Frontal and temporal lobar masks from the Wake Forest University PickAtlas (Maldjian et al., 2004; Maldjian et al., 2003) were registered to each participant's FLAIR space using ANTs. The binary WMH segmentation from LST was then multiplied by the FLAIR-registered binary lobar mask to obtain WMH volume for frontal and temporal lobes.

ASL images

ASL data were processed using the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) (Shin et al., 2013) pipeline established at the University of California San Diego's Center for Functional Magnetic Resonance Imaging. CBFBIRN uses a combination of custom MATLAB (MathWorks, 1996) routines and various functions from Analysis of Functional Neuroimages (AFNI) (Cox, 1996) and FMRIB Software Library (FSL) (Smith et al., 2004) to quantify CBF and adjust for partial volume effects. MATLAB was used to form a mean ASL image from the average difference of the control and tag images. Voxelwise CBF calibration was performed using the proton density image to convert the ASL difference signal into physiological units (mL/100g/min). In addition, slice timing delays were accounted for, making the post-labeling delay slice specific. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. Tissue segmentation was performed using FSL's Automated Segmentation Tool (FAST) algorithm to define CSF, gray matter (GM), and white matter (WM) regions. The high-resolution T1-weighted image and partial volume segmentations were registered to ASL space using AFNI's 3dAllineate program. To correct for partial volume effects and ensure that CBF values were not influenced by decreased perfusion in the WM or increased volume of CSF, we used a linear regression method (Asllani et al., 2008) with a 5x5 regression kernel to obtain corrected GM CBF measurements. For each participant's partial volume corrected quantified CBF map (in units of mL/100 g tissue/min), voxels with negative intensities were replaced with zero.

FreeSurfer was used to generate *a priori* anatomical ROIs for the CBF data. Briefly, for each participant, the FreeSurfer formatted T1-weighted brain volume was registered to the ASL CBF-aligned T1-weighted anatomical image (the latter was derived as part of the CBFBIRN pipeline). The resulting co-registration matrix was used to align the FreeSurfer aparc+aseg segmentation volume to the ASL CBF-aligned T1-weighted image. The CBF-aligned FreeSurfer volumes were visually inspected to ensure proper alignment and were then downsampled to the resolution of the CBF ASL image. Mean CBF was then extracted for FreeSurfer ROIs.

Statistical analysis

Multiple linear regression models were used to examine the associations of continuous PA with cognitive functioning and MRI variables. Cognitive variables of interest included the memory and executive function composite scores described above. Cerebrovascular brain health variables of interest included a limited number of *a priori* ROIs to minimize the number of statistical analyses in an attempt to reduce susceptibility to type 1 errors. For WMH, we examined frontal and temporal WMH volumes. For CBF, we examined four ROIs (two frontal regions and two temporal regions) including: rostral middle frontal gyrus, medial orbitofrontal cortex, hippocampus, and inferior temporal cortices. As described above, we selected these specific ROIs given these regions have been shown to be implicated in cerebrovascular dysfunction in aging and dementia risk (Bangen et al., 2018; Yew et al., 2017).

Frontal and temporal WMH volumes were divided by total intracranial volume to correct for head size. The distribution of WMH volume (divided by total intracranial volume) was positively skewed, so a log-transformation was used to improve distribution normality. Each of the dependent variables (memory, executive function, regional WMH, regional CBF) were assessed in separate models. Two models were run for each dependent variable: one model including MVPA and all light PA as predictors and a second model additionally adjusting for age and accelerometer wear time. We selected covariates for inclusion in our models based on both theoretical and statistical considerations. We considered including sex and education as covariates in our models given expected associations with cognition and brain variables. However, in an effort to maximize statistical power and not overadjust our models, we did not include sex and education as covariates given they did not correlate with any of the dependent variables in our sample (all p-values > .05). Potential multicollinearity of the independent variables was assessed for all models. All variance inflation factor (VIF) values were < 1.3 and the all bivariate correlation coefficients between the independent variables were r's < .6 (Field, 2009). In order to address potential inflation of type I error due to multiple comparisons, false discovery rate (FDR) was controlled at 0.05 using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). Each set of analyses examining the same category of dependent variable was treated as an omnibus test with multiple comparisons correction separately applied for each (i.e., applied separately for the two cognitive measures, two WMH ROIs, and four CBF ROIs). All statistical analyses were conducted using the IBM SPSS Statistics for Macintosh, Version 28.0.

Results

Participant characteristics and accelerometer assessment

Descriptive data for clinical and demographic characteristics is shown in Table 1. On average, the sample was approximately 72 years and well-educated. The sample had relatively low vascular risk burden (i.e., the mean Framingham Stroke Risk Profile (D'Agostino et al., 1994) score indicated a 7% probability of having a stroke within the next 10 years). The mean score on a measure of global cognitive functioning was unimpaired (i.e., Dementia Rating Scale total score of 140 out of 144).

Participants were compliant with accelerometer wear during the assessment period. Accelerometer metrics and the amount of time participants spent on average within different activity categories are displayed in Table 2.

Table 1. Participant characteristics for the entire sample (N = 43)

	Mean	SD
Demographics		
Age (years)	71.77	4.19
Education (years)	16.86	2.21
Sex (% female)	74.40%	—
Race (% White)	93%	—
Framingham Stroke Risk Profile (%)	7.19	4.23
Cognitive measures		
Memory Composite z-score	0.00	0.80
Executive Composite z-score	0.00	0.75
MRI measures		
Frontal WMH volume (%)	0.16	0.29
Temporal WMH volume (%)	0.12	0.11
Rostral middle frontal gyrus CBF, ml/100g/min	45.87	13.61
Medial orbitofrontal cortex CBF, ml/100g/min	40.80	17.06
Hippocampal CBF, ml/100g/min	40.03	11.52
Inferior temporal CBF, ml/100g/min	36.44	15.21

Note. PA = physical activity; min = minutes; WMH = white matter hyperintensities; CBF = cerebral blood flow. WMH variables expressed as percent are normalized by total intracranial volume to correct for head size and then multiplied by 100. Note that analyses were performed on log transformed WMH variables although descriptive statistics are shown here for non-transformed data.

Table 2. Accelerometer metrics

Variable	Mean	Standard deviation	Minimum	Maximum
Days of wear	7.40	1.28	4.00	10.00
Daily minutes of wear	910.82	74.19	782.50	1105.20
Total accelerometer wear time (min)	6733.23	1307.11	3913.00	11052.00
Sedentary time min/day (CPM 0-99)	585.37	109.22	350.12	844.71
All light PA min/day (CPM 100–1951)	301.65	81.50	136.50	524.33
Moderate to vigorous PA min/day (CPM ≥1952)	23.80	17.36	1.38	60.17

Note. CPM=Accelerometer counts per minute; min = minutes; PA = physical activity.

Associations of continuous PA with measures of cognition

In models including MVPA and all light PA as predictors, higher MVPA was uniquely associated with better performance on memory and executive functioning measures. See Table 3 and Figure 1. As shown in Table 3, all light PA was not uniquely associated with performance on cognitive measures. In models additionally adjusted for age and accelerometer wear time, findings remained similar. That is, higher MVPA was associated with better memory and executive functioning. These results survived correction for multiple comparisons.

Associations of PA with measures of brain health

In models including MVPA and all light PA as predictors, higher continuous MVPA was uniquely associated with lower frontal WMH volume but not temporal WMH volume. See Table 4 and Figure 2. In models additionally adjusted for age and accelerometer wear time, findings were attenuated and there was no longer a significant association between MVPA and frontal WMH volume. All light PA was not significantly associated with WMH volume.

Higher continuous MVPA was not significantly associated with regional CBF. In contrast, there was a unique association between greater all light PA and higher inferior temporal CBF. In models additionally adjusted for age and accelerometer wear time, findings

Table 3. Multiple linear regression models for association of physical activity with cognitive performance (N = 43)

	Memory			Executive function		
	β	t	p	β	t	p
Model 1						
All Light PA	.030	0.200	.843	−.028	−.193	.848
MVPA	**.356**	**2.373**	**.023**	**.456**	**3.170**	**.003**
Model 2						
All Light PA	.067	−.361	.720	−.004	−.027	.979
MVPA	**.333**	**2.061**	**.046**	**.413**	**2.536**	**.015**

Note. Abbreviations: PA = physical activity; MVPA = moderate to vigorous physical activity. Wear time denotes total time the accelerometer was worn. Model 1: All light PA and MVPA as independent variables. Model 2: Additionally adjusted for age and accelerometer wear time. Statistically significant (*p* < 0.05) results appear in bold font. These results survived correction for multiple comparisons.

Table 4. Multiple linear regression models for association of physical activity with regional WMH volume (N = 43)

	Frontal WMH			Temporal WMH		
	β	t	p	β	t	p
Model 1						
All Light PA	−.013	−.089	.930	.029	.187	.852
MVPA	**−.342**	**−2.262**	**.029**	−.277	−1.784	.082
Model 2						
All Light PA	−.122	−.899	.374	−.078	−.535	.596
MVPA	−.130	−.907	.370	−.076	−.492	.626

Note. β = standardized coefficient; PA = physical activity; MVPA = moderate to vigorous physical activity; WMH = white matter hyperintensities. Wear time denotes total time the accelerometer was worn. Model 1: All light PA and MVPA as independent variables. Model 2: Additionally adjusted for age and accelerometer wear time. Statistically significant (*p* < 0.05) results appear in bold font.

remained similar and there was a unique association between higher all light PA and greater rostral middle frontal and inferior temporal CBF. See Table 5 and Figure 3. The result for inferior temporal CBF survived correction for multiple comparisons although the finding for rostral middle frontal CBF did not. In addition, there was one CBF outlier (i.e., regional CBF values >3 standard deviations from the sample mean), however, excluding this one participant did not change the pattern or significance of results.

Discussion

This study sought to advance the literature on PA prescriptions to promote brain health by investigating if objectively measured PA is associated with cognitive performance and markers of cerebrovascular health (regional CBF and WMH volume) in a sample of cognitively healthy, community-dwelling older adults. Greater time spent in MVPA was uniquely associated with better performance on memory and executive functioning tasks. Higher MVPA was also associated with lower frontal WMH volume although the finding was attenuated and no longer significant after additionally adjusting for age and accelerometer wear time. MVPA was not associated with CBF. Higher time spent in all light PA was uniquely associated with higher inferior temporal CBF. However, higher time spent in light PA was not uniquely associated with cognitive performance or WMH volume. Although findings are preliminary and should be replicated in larger samples with longitudinal follow-up, the pattern of results suggest that MVPA

Table 5. Multiple Linear regression models for association of physical activity with regional CBF (N=43)

	rMFG CBF			mOFC CBF			Hippo CBF			InfTemp CBF		
	β	t	p	β	t	p	β	t	p	β	t	p
Model 1												
All Light PA	.291	1.933	.060	.185	1.167	.250	.112	.702	.487	**.419**	**2.861**	**.007**
MVPA	.163	1.086	.284	−.107	−.678	.501	−.123	−.774	.444	−.159	−1.088	.283
Model 2												
All Light PA	**.354**	**2.280**	**.028**	.237	1.581	.122	.031	.192	.849	**.477**	**3.372**	**.002**
MVPA	.049	.295	.770	−.239	−1.504	.141	−.030	−.176	.861	−.290	−1.932	.061

Note. Abbreviations: PA = physical activity; MVPA = moderate to vigorous physical activity; rMFG = rostral middle frontal gyrus; CBF = cerebral blood flow; mOFC = medial orbitofrontal cortex; hippo = hippocampal; InfTemp = inferior temporal gyrus. Wear time denotes total time the accelerometer was worn. Model 1: All light PA and MVPA as independent variables. Model 2: Additionally adjusted for age and accelerometer wear time. Statistically significant ($p < 0.05$) results appear in bold font. The results for inferior temporal CBF survived correction for multiple comparisons although the finding for rostral middle frontal CBF did not.
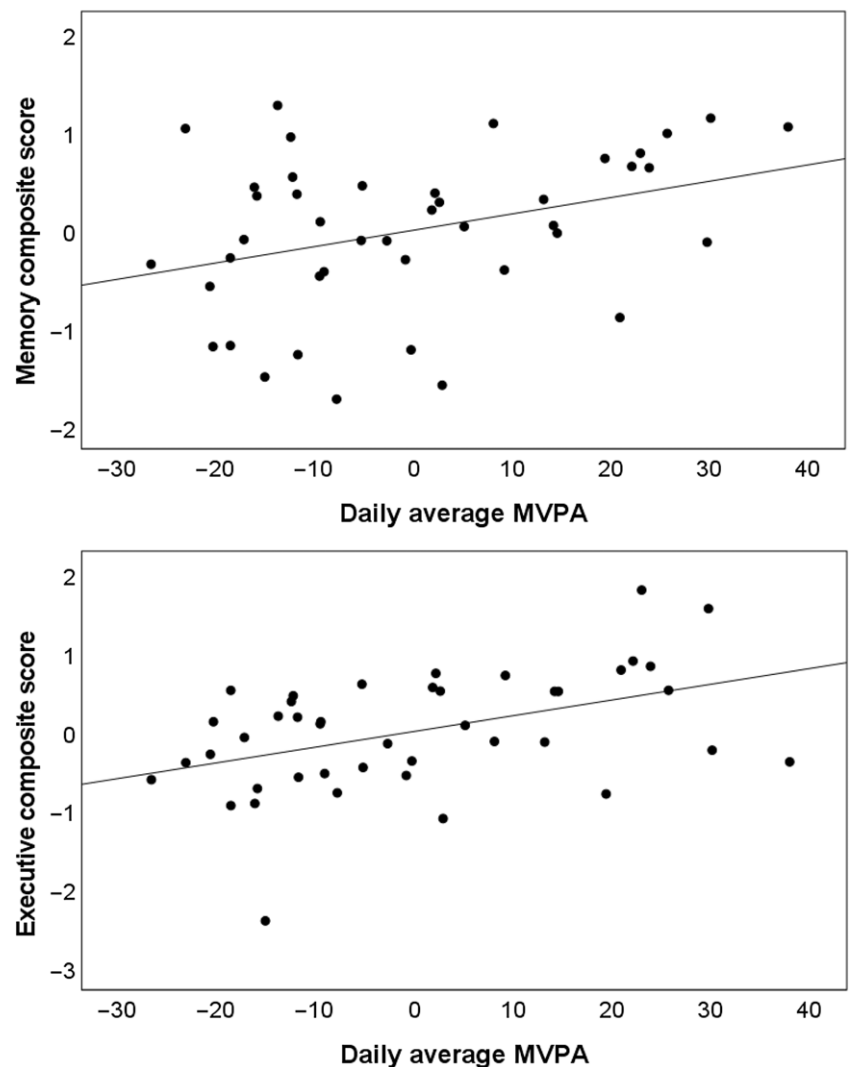

Figure 1. Partial regression plots for the association of moderate to vigorous physical activity (MVPA) and cognitive performance for episodic memory (top panel) and executive function (bottom panel) adjusting for all light physical activity.

may be beneficial for cognitive functioning and both MVPA and all light PA may be protective against decline in aspects of cerebrovascular health.

WMH are often seen as incidental findings on neuroimaging (Wardlaw et al., 2015). However, growing research clearly demonstrates their clinical importance. WMH become more common with advanced aging (DeCarli et al., 2005; Morris et al., 2009) and until relatively recently were often considered to be part of

normal aging (Wardlaw et al., 2015), although their prevalence is highly variable and increases with vascular risk factors including hypertension (Dufouil et al., 2003; Maillard et al., 2012), diabetes (Werhane et al., 2021) and smoking (Gons et al., 2011). A meta-analysis of 22 studies found that WMH were associated with a faster decline in global cognition, executive function, and processing speed as well as a 2-fold increase in the risk of developing dementia and a 3-fold increase in risk of stroke (Debette &
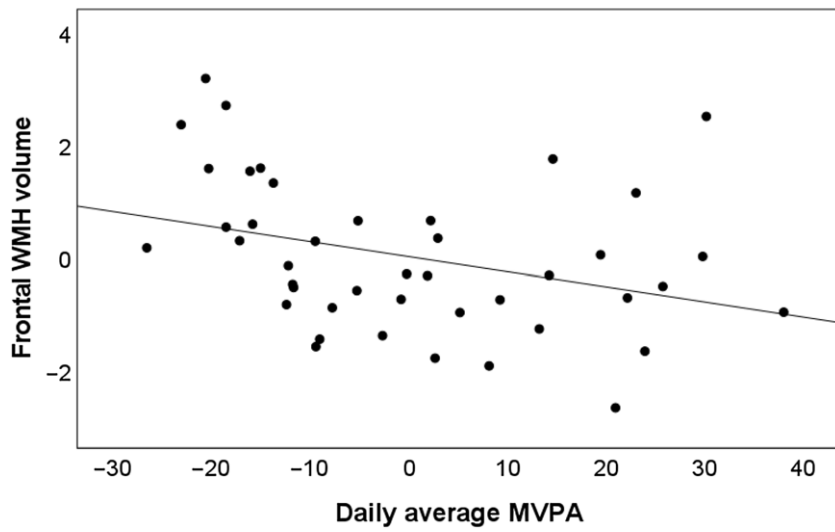
Figure 2. Partial regression plot for the association of moderate to vigorous physical activity (MVPA) and frontal white matter hyperintensity (WMH) volume adjusting for all light physical activity.
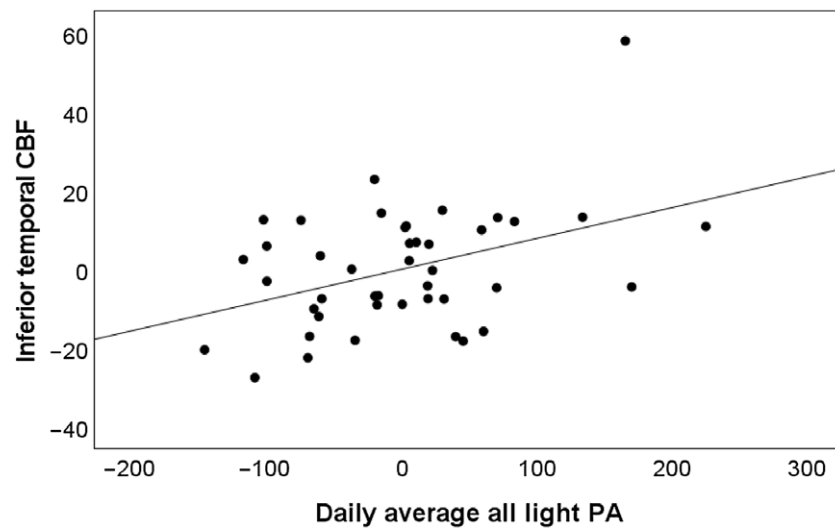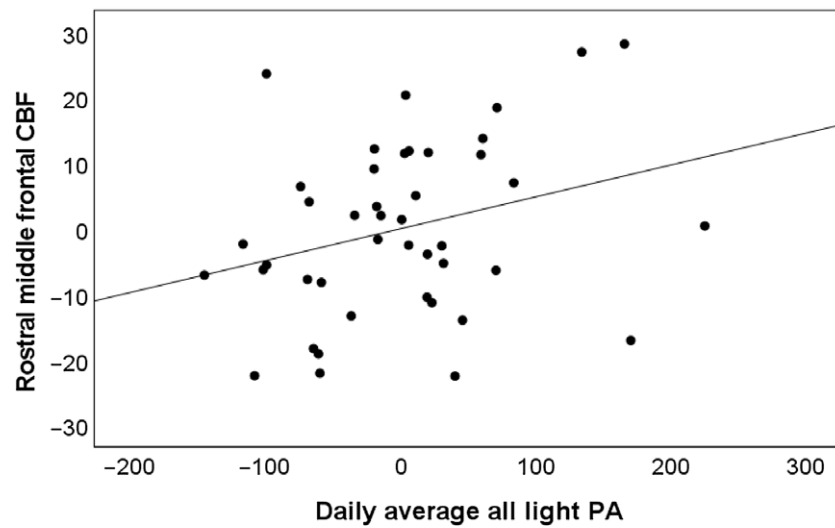

Figure 3. Partial regression plots for the association of all light physical activity (PA) and cerebral blood flow (CBF) in rostral middle frontal (top panel) and inferior temporal regions (bottom panel) adjusting for moderate to vigorous physical activity.

Markus, 2010). In addition, we have previously shown that baseline higher WMH volume predicts conversion from normal cognition to mild cognitive impairment (Bangen et al., 2018) as well as functional decline (Bangen et al., 2020).

Our findings are in line with previous studies suggesting that PA may be protective against WMH (Bronas et al., 2019; Gow et al., 2012; Tseng et al., 2013; Yu et al., 2021). Although it should be noted that the literature linking PA and WMH has been mixed (Sexton et al., 2016; Torres et al., 2015) with some studies finding no association between PA and WMH (Soldan et al., 2022). Notably, although WMH have often been thought of as irreversible and many longitudinal studies focus on slowing or halting progression of WMH, there is some evidence that WMH may not always be permanent. Early WMH may reflect shifts in water content and not just permanent myelin loss or axonal damage. Indeed, some studies of individuals who have had a stroke have shown WMH reduction over time (Moriya et al., 2009; Wardlaw et al., 2017). Elucidating the mechanisms by which PA affects white matter health needs further study (Soldan et al., 2022). Some evidence suggests that exercise-induced brain-derived neurotrophic factor (BDNF) and endothelial growth factor (Gaitán et al., 2021; Nicolini et al., 2021; Soldan et al., 2022) may enhance axon regeneration and also increase CBF and neurogenesis, suggesting multiple potential ways PA could improve white matter integrity (Trigiani & Hamel, 2017). Future randomized clinical trials involving longitudinal interventions are needed to establish whether PA may prevent progression or development of WMH or even possibly reverse WMH, thereby potentially mitigating their effects on cognitive and functional abilities.

It was somewhat unexpected that in the current study MVPA did not relate to CBF. We have previously shown that MVPA is associated with greater frontal CBF whereas sedentary time had an inverse association with CBF (Zlatar et al., 2019). Whereas WMH development are generally thought of as an insidious process, results across studies examining ASL MRI among older adults at risk for cognitive impairment have suggested that associations with CBF may be complex, with some studies reporting increases in CBF and others reporting decreases in CBF, while others suggest both depending on the regions or risk factors examined (Bangen et al., 2012; Wierenga et al., 2012). Increased resting CBF among older at-risk adults has often been interpreted as reflecting neurovascular dysregulation or possible compensatory mechanisms (Bangen et al., 2017). Findings from an 8-year longitudinal study using H(2)(15)O positron emission tomographic CBF suggested that CBF may increase to compensate for lower interregional neural communication resulting from white matter disruption (Kraut et al., 2008).

Given our strict inclusion criteria, our sample was comprised of cognitively unimpaired and medically healthy individuals. Our MVPA-CBF findings may have differed in a sample with greater vascular risk burden or if we had examined different brain regions. As described above, we selected a limited number of *a priori* ROIs to minimize the number of statistical analyses in an attempt to reduce susceptibility to type 1 errors. The specific *a priori* regions we examined were selected because they have been implicated in cerebrovascular dysfunction in aging and dementia (Bangen et al., 2018; Yew et al., 2017).

Given the observed associations of all light PA with CBF (but not cognition or WMH volume) and associations of MVPA with cognition and WMH volume (but not CBF), it is possible that different PA intensities have divergent associations with markers of brain health. Alterations in CBF may represent a relatively early or subtle change in cerebrovascular functioning that precedes the development of frank lesions such as WMH (Bangen et al., 2021; Zlokovic, 2011). Our findings suggest that lighter intensity PA may be more sensitive to subtle changes in cerebrovascular function (i.e., CBF), whereas MVPA may be more favorable in protecting against cognitive decline and development of frank lesions (i.e., WMH). Previous studies have reported associations between greater PA and reduced WMH volume (e.g., Tseng et al., 2013). However, in the present study, the association of MVPA and WMH was observed when we accounted for all light PA but attenuated and no longer significant when we additionally adjusted for age and accelerometer wear time. Future studies with larger samples and longitudinal data should further elucidate the association of different PA intensities with cognition, CBF, and WMH as well as potential moderators of MRI-PA associations.

This study has limitations that should be considered when interpreting our findings and should be addressed in future studies. The cross-sectional design limits our ability to make causal interpretations and the relatively small sample size reduces statistical power to detect associations. Strengths of this study include the use of a well-characterized sample of cognitively unimpaired older adults, ASL MRI to assess CBF together with quantification of WMH volume, and accelerometry to objectively measure PA as it occurs in free-living environments.

Conclusion

Engaging in PA may be beneficial for cerebrovascular health (WMH, CBF) with greater MVPA in particular possibly preserving memory and executive function in otherwise cognitively healthy older adults. There may be differential effects of engaging in lighter activities and MVPA on MRI markers of cerebrovascular health although this needs to be confirmed in future studies. Specifically, lighter activities may be associated with subtle alterations in CBF whereas MVPA may be more sensitive to WMH. Furthermore, randomized controlled trials that test different levels of PA intensity are needed to elucidate cause-effect associations and dose-response patterns of PA with cognitive and brain health.

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