Physical Activity and Cerebral Small Vein Integrity in Older Adults

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ABSTRACT

SHAABAN, C. E., H. J. AIZENSTEIN, D. R. JORGENSEN, R. L. M. MAHBUBANI, N. A. MECKES, K. I. ERICKSON, N. W. GLYNN, J. METTENBURG, J. GURALNIK, A. B. NEWMAN, T. S. IBRAHIM, P. J. LAURIENTI, A. N. VALLEJO, and C. ROSANO. Physical Activity and Cerebral Small Vein Integrity in Older Adults. *Med. Sci. Sports Exerc.*, Vol. 51, No. 8, pp. 1684–1691, 2019. Identifying promoters of cerebral small vein integrity is important to counter vascular contributions to cognitive impairment and dementia. **Purpose:** In this preliminary investigation, the effects of a randomized 24-month physical activity (PA) intervention on changes in cerebral small vein integrity were compared to those of a health education (HE) control. **Methods:** Cerebral small vein integrity was measured in 24 older adults (n = 8, PA; n = 16, HE) using ultra-high field MRI before and at the end of the 24-month intervention. Deep medullary veins were defined as straight or tortuous; percent change in straight length, tortuous length, and tortuosity ratio were computed. Microbleed count and white matter hyperintensities were also rated. **Results:** Accelerometry-based values of PA increased by 17.2% in the PA group but declined by 28.0% in the HE group. The PA group, but not the HE group, had a significant increase in straight vein length from baseline to 24-month follow-up (P = 0.02 and P = 0.21, respectively); the between-group difference in percent change in straight length was significant (increase: median, 93.6%; interquartile range, 112.9 for PA; median, 28.4%; interquartile range, 90.6 for HE; P = 0.07). Between group differences in other markers were nonsignificant. **Conclusions:** Increasing PA in late-life may promote cerebral small vein integrity. This should be confirmed in larger studies. **Key Words:** VASCULAR CONTRIBUTIONS TO COGNITIVE IMPAIRMENT AND DEMENTIA, CEREBRAL SMALL VESSEL DISEASE, RANDOMIZED CONTROLLED TRIAL, ULTRA-HIGH FIELD MRI, SUSCEPTIBILITY-WEIGHTED IMAGING

Loss of cerebral small vessel integrity is increasingly recognized as a key vascular contribution to cognitive impairment and dementia, including Alzheimer's disease (AD) (1–4). Although studies evaluating small vessel integrity generally focus on cerebral parenchymal changes of presumed vascular origin or arterial-side changes, the integrity of the venous side of the circulation is also vitally important. Cerebral small vein integrity is critical for healthy blood flow; the veins are the site of initial inflammatory response, which may cause alterations in interstitial fluid content and damage vessels and brain parenchyma; and animal work has suggested that the venous side may be the site of initial aβ deposition (5). Abnormalities in deep medullary venous morphology, including tortuosity, have been shown in association with AD in post mortem (6) and *in vivo* human studies (7), as well as in animal models (8).

Tortuosity of deep medullary veins has high pathobiological relevance. First, tortuosity of these veins, straight in normal healthy conditions, is the end-result of pathological processes (9). Second, it commonly cooccurs with small vessel disease (10). Finally, the veins' tortuosity is strongly related with altered cerebral blood flow (11). Thus, small vein integrity could represent a new intervention target for AD-related cognitive impairment.

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Physical activity (PA) has gained interest as a candidate promoter of cerebrovascular integrity. In addition to well-known effects on the hippocampus (12,13), recent work suggests that PA may have effects on neuroimaging markers of lesions of presumed vascular origin (14,15). Most existing studies use *indirect* markers of *late-stage* cerebral small vessel disease as opposed to examining the influence of PA directly on the integrity of the cerebral small vessels themselves. This type of work has been limited to one small, observational study examining the relationship between self-reported aerobic activity level over the past 10 yr (high vs low) and health of cerebral arteries of healthy older adults by magnetic resonance angiography (16). Critically missing from the literature are longitudinal observational studies with prospective, repeated measures of PA and cerebral small vessel integrity as well as well-controlled interventions of PA on cerebral small-vessel integrity as are studies with more rigorous measures of PA. Thus, the effects of PA on *in vivo* measures of early stages of cerebral small vessel abnormalities are currently unknown.

Several growth factors have been proposed as potential mechanisms underlying the beneficial effects of PA on brain vasculature, including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). Vascular endothelial growth factor is a well-recognized angiogenic factor (17). Emerging evidence from animal models also suggests an angiogenic role for BDNF (18,19) in addition to its neurogenic effects (20,21). We have recently shown in a cross-sectional analysis that lower peripheral blood levels of VEGF are associated with a higher tortuosity ratio of deep medullary veins in older adults (22). Whether PA and PA-related changes in BDNF and VEGF are associated with changes in cerebral small vein integrity has not been tested.

In this preliminary investigation, we conducted a secondary analysis of a randomized controlled trial (RCT) of 24-month PA versus health education (HE) control to evaluate the effects of PA on several markers of cerebral small vessel abnormalities. We have recently shown a beneficial effect of PA on hippocampal volume in this cohort (13). In this analysis, we hypothesized that the PA intervention would be associated with less morphological change of deep medullary veins (e.g., less tortuosity) and less accrual of white matter hyperintensities (WMH) and microbleeds. Our secondary exploratory aim was to assess the association between PA-related changes in BDNF, VEGF, and cerebral small vein integrity.

METHODS

Participants. Study participants were from the Lifestyle Interventions and Independence for Elders (LIFE) RCT in which 1635 participants were randomized either to PA or HE. The study demonstrated a beneficial effect of the PA intervention on the prevention of major mobility disability (23). Participants in this analysis are from the magnetic resonance imaging (MRI) substudy carried out at the Pittsburgh field center. Both the parent and substudy inclusion/exclusion criteria have been previously reported (22,23). Briefly, participants had to be sedentary, community-dwelling, 70 to 89 yr old, at risk of mobility disability as demonstrated by a Short Physical Performance Battery (24) score of ≤9, but able to walk 400 m, and agreeable to completing an MRI at study baseline and at the 24-month follow-up visit. Participants were excluded if they were cognitively impaired based on the Modified Mini-Mental State Examination (25), determined unsafe to participate in the study based on medical record review, or if they met any MRI exclusion criteria, such as claustrophobia or metal in the body, that could interfere or be of a safety concern for the MRI. The University of Pittsburgh Institutional Review Board reviewed and approved the study protocol (institutional review board protocol numbers: PRO09090386 and PRO15010473), and informed consent was carried out before completion of any study procedures.

Intervention. Participants were randomized either to PA intervention or HE control. Physical activity was multicomponent, involving moderate-intensity aerobic activity (walking), light resistance training, and flexibility exercises. Physical activity training included two clinic visits per week and 3 to 4 $d \cdot wk^{-1}$ of at-home PA. Moderate-intensity walking was defined based on a rate of perceived exertion of 13/"somewhat hard" on the Borg scale (26). Based on the *2008 Physical Activity Guidelines for Americans* (27), PA group participants worked to achieve a goal of 150 min of moderate-intensity walking per week. The HE group received healthy aging classes weekly for the first 6 months and twice monthly thereafter. Classes covered topics including health screenings, preventive services, and the like, and specifically avoided PA-related topics. For a detailed description of the intervention, see Pahor et al. and Fielding et al. (23,28).

Physical activity. Physical activity was characterized by participation in the PA intervention as well as minutes of moderate PA. In a subgroup ($N = 14$, $n = 7/8$ in the PA group, $n = 7/16$ in the HE group), accelerometry was collected as an objective measure of PA. At study baseline, 6, 12, and 24 months, daily minutes of moderate PA were measured across 7 d using the GT3X hip-worn accelerometer by Actigraph (Pennsacola, FL). Moderate PA by accelerometry was defined by a 760-count per minute cutoff (23).

Sample characteristics. Age, race, and sex were self-reported by participants. *Apolipoprotein E* (*APOE*) genotyping was carried out using TaqMan (Applied Biosystems, Life Technologies, Foster City, CA) and pyrosequencing (29). We present results here for *APOE4* allele presence.

Growth factors. Blood was collected while participants were fasting and was centrifuged at 1600*g* for 15 min at 4°C after clotting at room temperature for 30 to 60 min. Serum was then aliquoted and stored at ≤−70°C until analysis. We used Luminex with multiplex kits (EMD Millipore Human Neurodegenerative Disease Panel, Danvers, MA; Bio-Rad Human Cancer Panel, Hercules, CA) to test BDNF and VEGF levels. We used two sets of standard curves to determine concentrations, and standardized procedures have been validated to calculate growth factor values (30).

Cerebral small vein integrity. We traced deep medullary veins in periventricular regions of interest in both cerebral hemispheres on susceptibility-weighted MRI at ultrahigh field strength (7 T) based on our previously reported method (22). Deep medullary veins are typically straight, with tortuosity, the result of a pathological process (9); therefore, veins were characterized as either straight or tortuous. Using a consensus method with three raters (C.E.S., D.R.J., N.A.M.), we determined total straight and tortuous venous length across both hemispheres for each participant at both baseline and 24-month follow-up. To summarize all information in one metric, we also calculated the tortuosity ratio for each participant. It was defined as total tortuous venous length over total straight venous length. Raters were blinded to intervention assignment during vein tracing and consensus meetings.

Microbleeds. Two raters (N.A.M., E.T.) counted microbleeds across 64 axial slices on 7-T susceptibility-weighted imaging after our previously published method (22) and Greenberg et al. (31). Raters came to an agreement on the counts through a consensus process and were blinded to intervention assignment.

White matter hyperintensities. Using our method for analyzing WMH on T2-weighted MRI and Magnetization Prepared Rapid Acquisition Gradient Echo at 7 T (22) WMH were characterized by two raters (CR, HJA) using a consensus process. Ratings ranged from 0 to 3 (none to severe) based on a modified Fazekas rating scale (32). Raters were blinded to intervention assignment during rating and consensus meetings.

Other variables. Certified raters administered the Modified Mini-Mental State Examination (25). This is a global measure of cognition. The score ranges from 0 to 100 with higher scores indicating better performance. The 4-m walk from the Short Physical Performance Battery was used to calculate gait speed in meters per second. Participants were asked to walk at their usual pace.

Statistical analysis. Differences between the PA and HE group were evaluated to determine whether randomization of baseline variables was held within this substudy. Differences between the group with MRI at both study baseline and 24-month follow-up and the group with MRI at baseline only were also evaluated. For each of these comparisons, nonparametric tests, including the Mann-Whitney U test and χ^2 tests were used.

To account for baseline values in analyses, percent change from baseline to 24 months was computed for all vein outcomes. These variables were calculated for each individual as (follow-up − baseline)/baseline × 100. Thus, a positive percent change indicates an increase from baseline to follow-up, whereas a negative percent change indicates a decline from baseline to follow-up. We calculated summary statistics for baseline, 24-month follow-up, and percent change as median (interquartile range [IQR]). Nonparametric tests of median comparisons were used to evaluate differences from baseline to 24 months within intervention groups and differences in percent changes between intervention groups for vein outcomes. Variables indicating worsening microbleed count and WMH grade were created. We defined worsening as present if the 24-month follow-up microbleed count or WMH grade was greater than the baseline value for that variable. Fisher's exact tests were used to assess differences in worsening microbleed count and WMH grade by intervention group.

We visually inspected scatterplots of associations of vein outcomes with PA. Given the small sample size, we repeated the plots with the most extreme values withheld to confirm that the direction of association was maintained. Spearman partial correlations were used to assess relationships of percent change in vein outcomes with PA adjusting one at a time for percent change in BDNF and VEGF. As a sensitivity analysis, we repeated these correlations of percent changes of vein outcomes with total minutes of moderate PA by accelerometry. For this analysis, the PA variable was a cumulative exposure variable to minutes of moderate PA created by summing accelerometry minutes of moderate PA across all study visits. Finally, we carried out exploratory analyses with growth factors. Percent change variables were created and nonparametric tests of median comparisons within and between intervention groups were carried out in the same way as with the vein outcomes. For any percent change vein outcome found to be related to PA, we visually inspected scatterplots of the percent change vein outcome by the percent change in growth factors across the full combined study sample. These were repeated with extreme values withheld. We used Spearman correlations to assess relationships of percent change in relevant vein outcomes with percent change in growth factors across the full sample. These were repeated as partial correlations adjusting for PA. Due to the small sample size, alpha was set at 0.10 to reduce likelihood of false negatives. When studies are preliminary and exploratory in nature, adjustment for multiple comparisons is likely to result in false negatives and abandonment of potentially promising but nascent lines of inquiry (33). Thus, to preserve interesting results in some of the earliest work in this area, we have not adjusted for multiple comparisons. Statistical analysis was performed in SAS version 9.4 (34).

RESULTS

This study sample consisted of 24 participants who had 7-T MRI at both baseline and 24-month follow-up. Eight were randomized to PA intervention, and 16 were randomized to HE control. Figure 1 illustrates the participant flow. Overall, the sample had a median (IQR) age of 76.0 (6.7), was 58.3% non-Hispanic white, and was 83.3% female. Medians and IQR or numbers and percentages of baseline characteristics are presented in Table 1. The PA and HE groups were well balanced on demographic and general health characteristics. Similarly, participants with MRI at baseline only were not significantly different from those with MRI at baseline and 24-month follow-up (see Table, Supplemental Digital Content 1, Baseline characteristics in those with and without follow-up venous outcomes, http://links.lww.com/MSS/B545). Moderate PA minutes by accelerometry increased by 17.2% in the PA group but declined by 28.0% in the HE group. Regarding

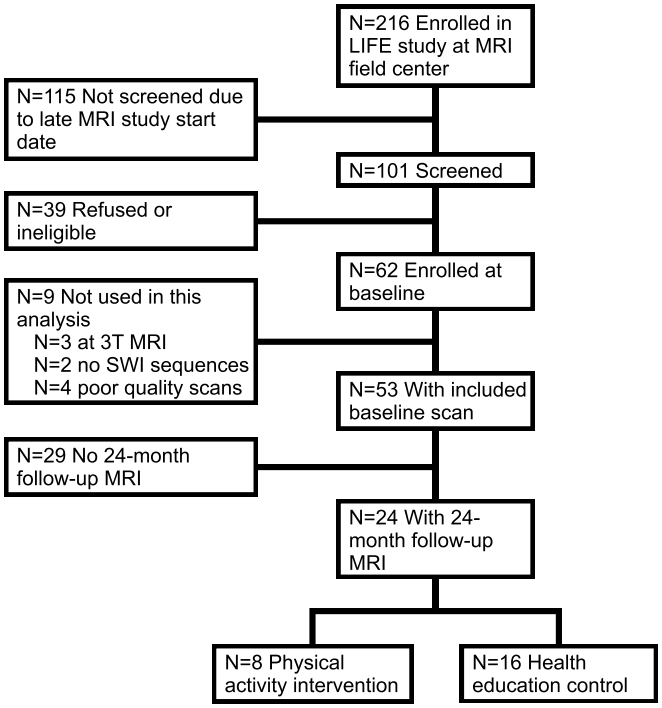

FIGURE 1—Study participant flow diagram.

the cumulative totals, the PA group had a median of 158.8 min of total daily moderate PA across all study visits, whereas the HE group had 86.7 total PA minutes.

Figure 2 shows illustrations of baseline and 24-month follow-up vein tracings by one rater in one participant from each intervention group. The PA group, but not the HE group, had a significant percent increase in straight length from baseline to 24-month follow-up ($P = 0.02$ and $P = 0.21$, respectively; Table 2). Most participants in the PA group had an increase in straight venous length from baseline to the 24-month follow-up (Fig. 3). There was a significant between-group difference in percent change of straight vein length, such that the PA group had a greater percent increase than the HE group ($P = 0.07$; Table 2).

Tortuosity ratio declined from baseline to follow-up by 33.2% within the PA group and 10.8% within the HE group. There were no significant within or between group differences for percent change in tortuous length or tortuosity ratio. Physical activity did not have a significant effect on worsening microbleed count or WMH grade. Approximately 42.9% of the PA group and 41.7% of the HE group had a worsening microbleed count (Fisher's exact $P > 0.99$). None of the PA group had a worsening WMH grade, whereas 18.8% of the HE group worsened by at least one WMH grade (Fisher's exact $P = 0.53$; Fig. 3).

The PA intervention was correlated with percent increases in straight venous length, and adjusting for percent change in BDNF and VEGF did not attenuate this relationship (Table 3). The PA intervention was not significantly associated with percent change in tortuous venous length or tortuosity ratio. These associations remained similar in sensitivity analyses using total moderate PA minutes by accelerometry in lieu of intervention group assignment; the association of PA with increases in straight length remained significant (unadjusted $\rho = 0.499$, $P = 0.07$), whereas the association of PA minutes with decreases in tortuosity ratio became significant (unadjusted $\rho = -0.538$, $P = 0.05$). *APOE4* presence was not significantly related to any of the vein outcomes.

Within- and between-group differences in BDNF and VEGF were not significant ($P > 0.1$ for all; See Table, Supplemental Digital Content 2, Impact of the PA intervention on growth factors, http://links.lww.com/MSS/B546). Percent changes in BDNF were positively correlated with percent changes in straight venous length ($\rho = 0.404$, $P = 0.07$), and

TABLE 1. Baseline characteristics in the LIFE study.

	PA, $n = 8$		HE, $n = 16$		P
Age (yr)	74.3	(5.5)	76.1	(6.9)	0.98
Race, non-Hispanic white	5/8	(62.5)	9/16	(56.3)	>0.99
Sex, female	7/8	(87.5)	13/16	(81.2)	>0.99
APOE4 allele presence	3/8	(37.5)	5/15	(33.3)	>0.99
Modified Mini-Mental State Examination	94.5	(10.5)	91.5	(8.0)	0.88
Gait speed, $m \cdot s^{-1}$	0.80	(0.27)	0.82	(0.20)	0.81
VEGF, $pg \cdot mL^{-1}$ [a]	482.9	(603.3)	391.3	(255.8)	0.77
BDNF, $pg \cdot mL^{-1}$ [a]	18,143.1	(23,782.0)	19,780.3	(24,036.0)	0.87
PA, min [b,c]	41.7	(14.9)	28.4	(37.6)	0.64
Severe WMH burden, [d] no./total no. (%)	3/8	(37.5)	3/16	(18.7)	0.71
No microbleeds, no./total no. (%)	5/8	(62.5)	7/14	(50.0)	0.58

Numbers are median (IQR) or no./total no. (%).
[a] $n = 15$, HE.
[b] Minutes of daily moderate PA by accelerometry.
[c] $n = 13$, HE.
[d] WMH rated as 0, none; 1, mild; 2, moderate; 3, severe.

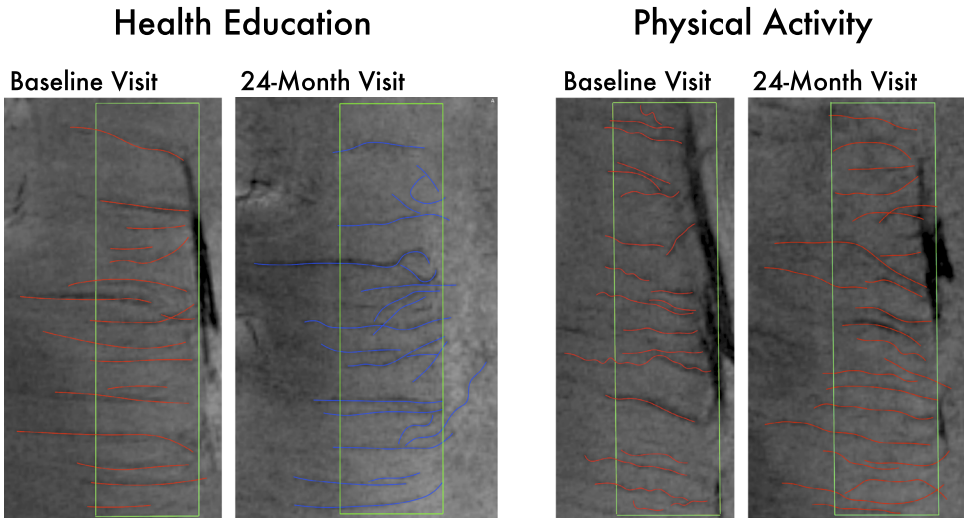

FIGURE 2—Illustrations of vein tracings by one rater on 7-T susceptibility-weighted MRI at baseline and 24-month follow-up in two study participants: one in the HE control group and one of the PA intervention group. The participant in the HE group had the following percent changes in their vein outcomes: straight vein length, 9.3%; tortuous vein length, 57.2%; and tortuosity ratio, 43.9%. The participant in the PA intervention had the following percent changes in their vein outcomes: straight vein length, 25.0%; tortuous vein length, −22.5%; and tortuosity ratio, −38.1%. Positive percent change indicates an increase from baseline to follow-up, whereas negative percent change indicates a decrease from baseline to follow-up.

adjusting for intervention arm did not attenuate this association. Percent change in VEGF was not associated with percent change in straight venous length.

DISCUSSION

In this preliminary study, participating in a 24-month randomized PA intervention was associated with greater percent increases in straight length of deep medullary veins than the HE control. This suggests that PA may promote cerebral small vein integrity in late adulthood, which could have downstream effects on cognition and behavior. If these results could be replicated in the context of a larger trial, we could more definitively determine if cerebral small vein integrity can be altered through PA. These results lend support to existing evidence that PA is associated with cerebral artery health and lower burden of neuroimaging lesions of presumed vascular origin (15,16,35,36). Associations of PA with the cerebral vasculature have been evaluated previously in a small, observational study comparing differences between high and low aerobic PA groups among healthy older adults (mean ages: 64 yr, high PA; 68 yr, low PA) (16). The PA assessment was based on self-report and generally mapped onto ≥180 min·wk^{-1} of moderate PA over the prior 10 yr (high PA) or <90 min of weekly PA with no specific PA program over the prior 10 yr (low PA). The results indicated lower tortuosity and increased numbers of vessels <0.6 mm in diameter in the high PA group versus low PA group. This study captured midsized arteries, whereas our study focused on small deep medullary veins.

We found no significant difference in worsening microbleed count by intervention group. More participants in the HE group demonstrated worsening WMH grade, although this was not statistically significant. Others have found that PA may be associated with lower burden or severity of WMH of presumed vascular origin, an indirect marker of later stage cerebral small vessel disease. A meta-analysis of nine studies (all with mean age >60) found a small protective effect of PA and physical fitness on WMH volume (15). Even among adults 40 to 65 yr old (mean age, 59 yr) with risk factors for AD, greater fitness was associated with reduced WMH burden (35). Although none of these studies evaluated impact on WMH progression, which would require multiple MRI, a secondary analysis of an RCT with preintervention and postintervention MRI found that resistance training reduced WMH progression among women with baseline WMH (mean age, 69 yr) (36). Our differing results may be due to our small sample size and lack of power to detect such small differences. Nevertheless, our results suggest that veins of even older, sedentary adults can be altered, and taken together, these results suggest that PA may have the capacity to promote cerebral small vessel integrity across several decades of midlife to late life.

TABLE 2. Impact of the PA intervention on venous outcomes.

	PA (n = 8)				HE (n = 16)				
	Baseline	Follow-Up	%Δ	P	Baseline	Follow-Up	%Δ	P	Between Arm, P
Straight venous length, mm	99.9 (49.9)	153.2 (82.7)	93.6 (112.9)	0.02	105.0 (104.8)	144.9 (131.6)	28.4 (90.6)	0.21	0.07
Tortuous venous length, mm	147.2 (93.3)	154.7 (52.0)	11.6 (64.5)	0.31	137.7 (69.5)	155.9 (79.9)	−12.9 (49.9)	0.63	0.41
Tortuosity ratio	1.4 (1.1)	1.1 (0.7)	−33.2 (63.5)	0.15	1.2 (1.1)	1.0 (1.5)	−10.8 (105.9)	0.98	0.38

Tortuosity ratio = total tortuous length/total straight length. Due to small samples sizes, all values presented as median (IQR) and nonparametric tests.

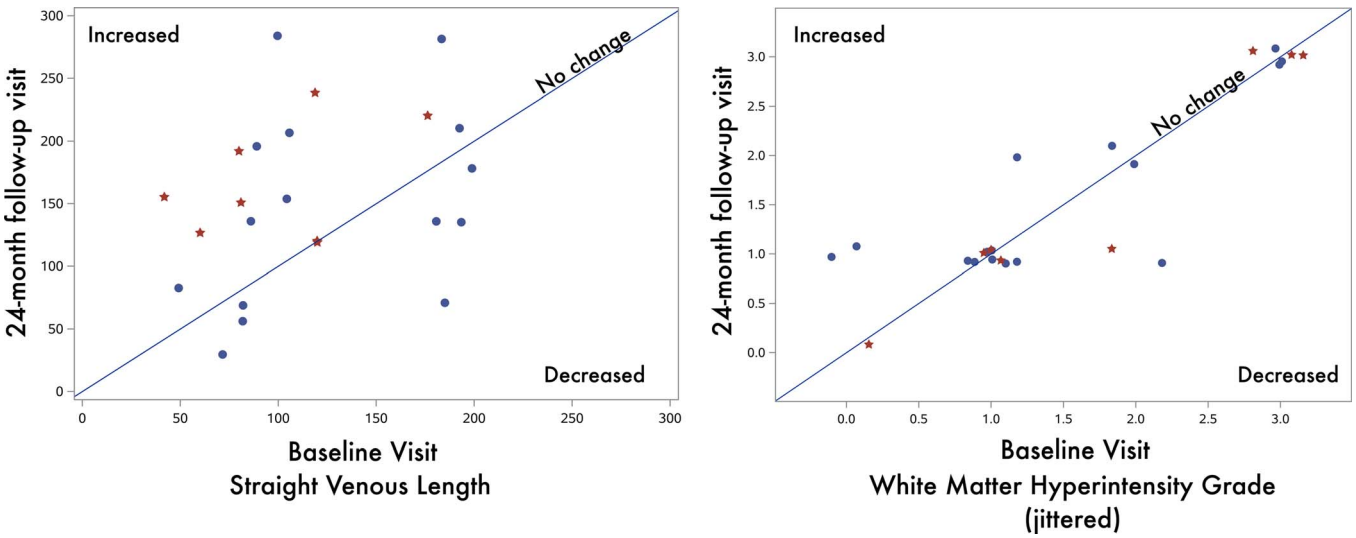

FIGURE 3—Change in straight venous length and WMH grade from baseline to 24-month follow-up by intervention group. *Red stars*, PA group; *blue circles*, HE control group. The *diagonal line* represents no change from baseline to 24-month follow-up. Above the line, increase; below the line, decrease. Note: The WMH grade figure is jittered to make all points visible because many were layered on top of one another. $n = 3$ from the HE group worsened in WMH grade, whereas $n = 0$ from the PA group worsened.

We found that straight venous length increased in both the PA and HE arms, although the increase in the HE arm was nonsignificant. This raises two questions. The first is whether PA can actually increase straight venous tissue as opposed to just reducing the loss of straight veins. In addition to promoting endothelial function, PA can also result in increased production or bioavailability of growth factors which could beneficially impact blood vessels (37). Although we did not find PA-related increased peripheral serum BDNF and VEGF, our results do not rule out increased central production or bioavailability of these factors. The second question is why both intervention groups would demonstrate increasing straight venous length. These results could be due to the exposure of the HE group to social activity. The HE classes were carried out in groups, potentially exposing HE participants to increased social activity, a factor beneficial for brain health (38,39). If this is the case, social activity may also be beneficial for cerebrovascular health. This result should be evaluated further in additional studies.

Interestingly, PA was associated with straight venous length but not tortuous venous length. This may indicate two separate pathophysiological pathways for the cerebral small veins: 1) decreasing straight venous length, which our results suggest PA may be able to counter; and 2) increasing tortuous venous length, which our results suggest PA does not counter. It is possible that through PA's action to generate rhythmic pulsing of the veins, either through the increased heart rate seen with aerobic activity or through rhythmic stretching of the vessels that may be seen with resistance activity, PA effectively maintains shear stress and flow parameters which help to promote endothelial function and nitric oxide production thus keeping the vessels healthy (37,40). It is feasible for this to preferentially benefit straight vessels as shear stress and cerebral blood flow are negatively altered in tortuous vessels (11). Reduced cerebral blood flow is one of the earliest changes in AD pathophysiology (41).

We found that *APOE4* was not associated with changes in vein outcomes over time. We had shown in our cross-sectional analyses that *APOE4* was associated with greater tortuosity ratio (22). Together these results suggest that *APOE4* is associated with one's starting point with regard to tortuosity, but not how rapidly tortuosity changes over time. This result should be confirmed in a larger study with multiple MRI over time.

Although we found no difference in BDNF between the intervention groups, we found that percent change in BDNF was positively associated with percent change in straight venous length. We interpret these results cautiously given that they are the result of exploratory analyses. If confirmed, these results may indicate that much like BDNF's beneficial impact on hippocampal volume (12) and functional connectivity (42), it may also be a promoter of cerebral small vein integrity. This supports animal evidence of BDNF's role in angiogenesis and vessel health (18,19), and work in humans finding that a genetic predisposition to lower and less efficient BDNF levels (43) was associated with greater WMH volume in older adults (mean age, 70 yr) (44).

Several limitations to this study should be kept in mind while interpreting these results. First, the IQR we present here for BDNF and VEGF are quite large. Serum markers like these

TABLE 3. Unadjusted and partial Spearman correlations assessing relationships of PA with venous outcomes.

	% Change Straight Venous Length		% Change Tortuous Venous Length		% Change Tortuosity Ratio	
	ρ	*P*	*ρ*	*P*	*ρ*	*P*
PA arm[a]	0.383	0.07	0.179	0.40	−0.192	0.37
Adjusted for %Δ BDNF[b]	0.426	0.06	0.247	0.30	−0.200	0.40
Adjusted for %Δ VEGF[b]	0.415	0.07	0.185	0.44	−0.191	0.42

[a] $n = 24$.
[b] $n = 21$.

are known to have high variance, and this variance can make differences hard to detect or significant values hard to trust. Future studies incorporating such markers should be designed with a large enough sample to account for this. Second, this study was a secondary analysis of an RCT and had a small sample size. Our sample was drawn from a larger RCT, was not significantly different from participants who received only a baseline MRI, and demonstrated maintained randomization of covariates. Nevertheless, we interpret these findings cautiously, and the results of this study should be tested in a larger study as part of a prespecified analytic plan.

There are several strengths of this study. First, our study design incorporated many advantages over existing studies. Although prior studies of PA and direct measures of cerebral small vessel integrity have been observational, ours is the first study examining the impact of a randomized controlled PA intervention on deep medullary veins. Most existing studies have been cross-sectional. However, the present study evaluated change over time through use of MRI at baseline and 24-month follow-up, allowing us to draw conclusions about change in vein integrity over time in response to the intervention. Moreover, our assessments of PA are more objective than retrospective self-report. We collected data on PA both by prospective random assignment to the PA intervention group and by cumulative moderate minutes of PA based on accelerometry. This eliminated recall bias and reduced misclassification of the exposure. Second, we studied a novel, direct vessel neuroimaging marker of cerebral small vein integrity as opposed to traditional late-stage markers of parenchymal damage of presumed vascular origin. This allows us a closer appreciation of the vessels themselves in studying promoters of cerebral small vessel integrity. Third, randomization and blinding were maintained in this substudy. Thus, the results of our primary analytic aim are controlled for potential confounding baseline factors.

Our study represents some of the earliest work in this important area of research. Future larger studies will be needed to confirm our results.

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The authors declare that they have no conflicts of interest. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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