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Physical Activity Predicts Microstructural Integrity in Memory-Related Networks in Very Old Adults

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Background. Although the beneficial effects of physical activity (PA) on memory and executive function are well established in older adults, little is known about the relationship between PA and brain microstructure and the contributions of physical functional limitations and chronic diseases. This study examined whether higher PA would be longitudinally associated with greater microstructural integrity in memory- and executive function-related networks and whether these associations would be independent of physical function and chronic diseases.

Methods. Diffusion tensor imaging was obtained in 2006–2008 in 276 participants (mean age = 83.0 years, 58.7% female, 41.3% black) with PA (sedentary, lifestyle active, and exercise active) measured in 1997–1998. Gait speed, cognition, depressive symptoms, cardiovascular and pulmonary diseases, hypertension, stroke, and diabetes were measured at both time points. Mean diffusivity and fractional anisotropy were computed from normal-appearing gray and white matter in frontoparietal and subcortical networks. Moderating effects of physical function and chronic diseases were tested using hierarchical regression models.

Results. Compared with the sedentary, the exercise active group had lower mean diffusivity in the medial temporal lobe and the cingulate cortex (β, *p* values: −.405, .023 and −.497, .006, respectively), independent of age, sex, and race. Associations remained independent of other variables, although they were attenuated after adjustment for diabetes. Associations between PA and other neuroimaging markers were not significant.

Conclusions. Being exercise active predicts greater memory-related microstructural integrity in older adults. Future studies in older adults with diabetes are warranted to examine the neuroprotective effect of PA in these networks.

Key Words: Brain aging—Physical activity—Neuroimaging—Epidemiology.

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FRONTOPARIETAL and subcortical networks are highly susceptible to changes in blood oxygenation levels (1,2) due to their watershed vascularization. Loss of structural integrity in these networks, specifically in dorsolateral prefrontal and hippocampal areas, is related to difficulties in memory and executive function and an increased risk of developing dementia (3). Because of exercise-induced vascularization (4–6), these networks may selectively benefit from the exposure to greater amounts of physical activity (PA).

It is well accepted that higher PA is associated with improved brain health (see review (7)) and these effects are stronger for memory and executive function than for motor control (see meta-analysis (8)). Neuroimaging studies indicate positive effects of PA on brain macrostructure and function (9–17). However, most of previous studies were cross-sectional designs and relied on low-resolution imaging and volumetric measurements of the brain. Data on the association between PA and brain microstructure are sparse, with one observational study indicating a positive association between PA and white matter (WM) integrity (14) and one intervention study reporting increases in WM integrity associated with increases with fitness from walking (18). Understanding the longitudinal association with brain microstructure in older adults may have important implications in designing interventions to preserve structural integrity by improving PA. Furthermore, it is important to differentiate

the effects of PA on gray matter (GM) and WM to understand the mechanisms of how PA influences brain integrity.

It is also critical to examine the contributions of physical functional limitations and chronic diseases, which are common in older adults. The relationships between PA, physical function, and chronic diseases become increasingly complex in late life. For example, PA may be beneficial for physical function and cardiovascular health, but in turn poor physical function and cardiovascular diseases (CVDs) may limit PA participation (19). Both PA and these potential modifiers are related to brain integrity (14).

This study quantified the associations between PA and microstructural integrity of GM and WM in a well-characterized cohort of very old adults, by accounting for health-related conditions. It was hypothesized that higher PA would be associated with greater microstructural integrity localized in frontal and medial temporal lobes important for memory and executive function compared with other regions, for example regions related to motor control. It was also hypothesized that these associations would be attenuated by physical function and chronic diseases.

Methods

Study Population

Participants were recruited from the Health, Aging and Body Composition Study, which began in March 1997 to assess the relationship between changes in body composition and health outcomes in a cohort of 3,075 community-dwelling older adults (52% women, 42% black) aged 70–79 years (20). A total of 325 participants at the Pittsburgh site received a brain magnetic resonance imaging (MRI) scan. Of 325, 276 had diffusion tensor imaging in 2006–2008 and PA measured in 1997–1998. The study protocol was approved by the University of Pittsburgh and all participants provided informed consent.

MRI Protocol and Markers

MRI scans were obtained at the MR Research Center of the University of Pittsburgh with 3Tesla Siemens TIM TRIO scanners equipped for echo-planer imaging using the protocol previously described (21). Magnetization-prepared rapid gradient echo images and fluid-attenuated inversion recovery images were acquired to obtain volumes of GM, WM, and WM hyperintensities, respectively. Diffusion tensor images were acquired using single-short spin-echo sequence with 12 directions and preprocessed using the FMRIB's Diffusion Toolbox (22) to remove unwanted distortions (voxel size = 2 mm × 2 mm; slice thickness = 3 mm). There were no pathological findings from MR images for this study as verified by a neuroradiologist.

Using the segmentation of GM, WM, and WM hyperintensities, the mean diffusivity (MD) and fractional anisotropy maps were restricted to normal-appearing GM and WM (21). Using Automated Labeling Pathway (23,24), neuroimaging markers in regions and tracts were identified based on the Automated Anatomical Labeling Atlas (25) and the Johns Hopkins University White Matter Atlas (26), respectively. Regions and tracts of interest were selected a priori, including medial temporal lobe, cingulate cortex, dorsolateral prefrontal cortex, posterior parietal cortex, and uncinate and superior longitudinal fasciculi (Figure 1). Other regions were examined as a comparison to the hypothesized regions and tracts, including striatum, primary sensorimotor cortex, and supplementary motor cortex. MD in regions of interest from left and right hemispheres was computed as the mean weighted by GM volume. Fractional anisotropy in tracts of interest from left and right hemispheres was computed as the mean.

Parenchyma atrophy was calculated by subtracting volumes of GM and WM from intracranial volume. The volume of WM hyperintensities normalized by total brain volume was dichotomized at the median due to a skewed distribution.

Physical Activity

PA was measured in 1997–1998 using a standardized questionnaire (27). Participants were categorized into sedentary, lifestyle active, and exercise active groups as previously defined (Supplementary Table 1) (28,29). Those with lifestyle activities less than 2,719 kcal/wk and exercise activities less than 1,000 kcal/wk were defined as sedentary (n = 39, 14.1%). Those with lifestyle activities more than 2,719 kcal/wk and exercise activities less than 1,000 kcal/wk were defined as lifestyle active (n = 148, 53.6%) and those with exercise activities more than 1,000 kcal/wk, regardless the amount of lifestyle activities, were defined as exercise active (n = 89, 32.2%). In additional sensitivity analyses, the sedentary group was defined by less than 2,719 kcal/wk of lifestyle activities only, because being sedentary most of the day and exercising regularly can also be considered as sedentary (30). Those with exercise activities more than 1,000 kcal/wk and lifestyle activities more than 2,719 kcal/wk were defined as exercise active.

Self-reported time spent walking in minutes per week was measured annually. Change was computed by subtracting walk time at study entry from walk time at time of MRI. The average time spent walking was computed using at least three valid values from study entry to time of MRI.

Other Measures of Interest

Gait speed at usual pace over 3, 4, or 6 m was measured at study entry, years 4 and 6, and time of MRI. Gait speed is a valid and reliable assessment of physical function for older adults (31). Slower gait speed is strongly associated with severity of health conditions and higher mortality risk (32,33). Change was computed by subtracting speed at study entry from speed at time of MRI. Annual percent change was computed by dividing relative change over 9 years by 9.

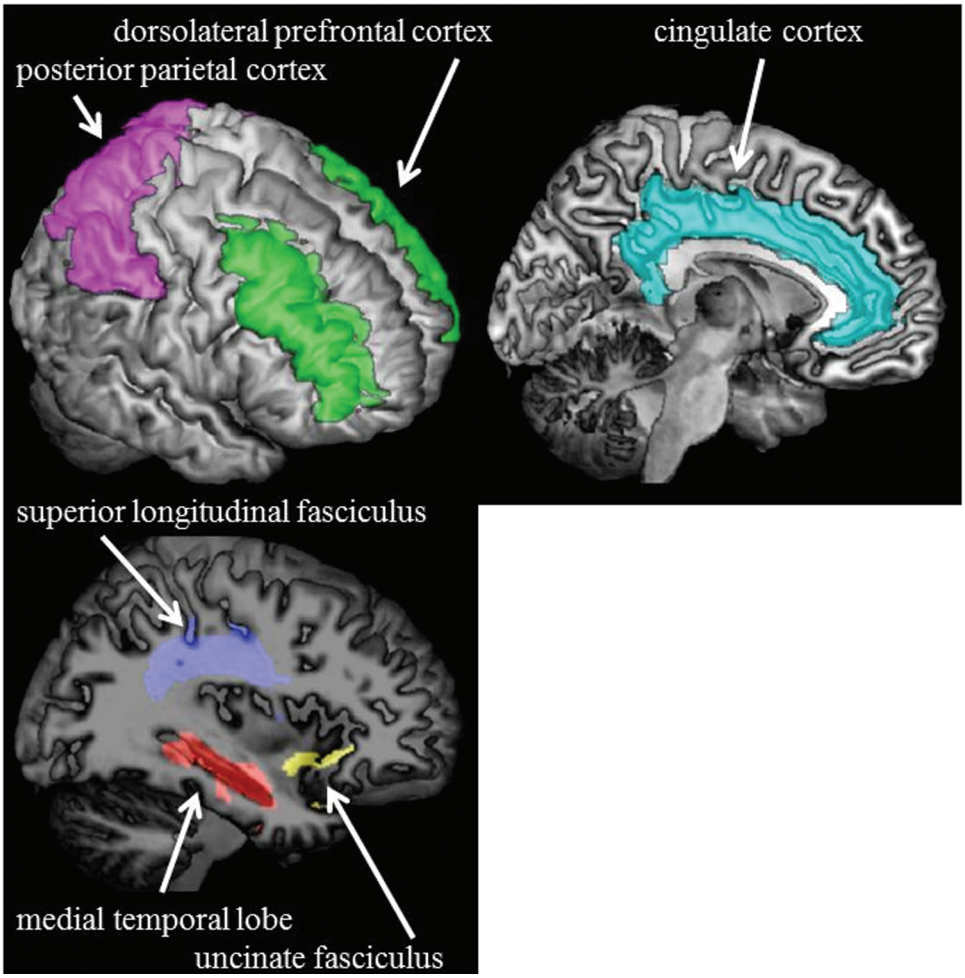

Figure 1. Regions and tracts of interest.

The Digit Symbol Substitution Test (DSST) was measured at study entry, years 5, 7, 8, and 9, and time of MRI. The modified mini-mental status examination (3MSE) was measured at study entry, years 3, 5, 7, and 9, and time of MRI. The Center for Epidemiologic Studies Depression Scale (CES-D) was measured at study entry, years 3–9, and time of MRI. Changes were computed by subtracting scores at study entry from scores at time of MRI. Annual percent changes were computed by dividing relative changes over 9 years by 9. The annual percent change was 0 when participants had 0 at study entry and time of MRI. For those with 0 values at study entry but nonzero values at time of MRI, 0 values at study entry were added to 1 in order to compute annual percent changes.

Chronic diseases, including prevalent CVD, pulmonary disease, hypertension, and diabetes, were obtained at study entry and time of MRI using prevalent disease algorithms according to self-reported diagnoses by physicians and records of medication use. Prevalent CVD was defined by self-report prevalent coronary heart disease or cerebrovascular disease. Prevalent pulmonary disease was defined by self-report or medication use. Prevalent diabetes and hypertension were defined by self-report and confirmed by medication use. Incident CVD and stroke were ascertained using annual self-report questionnaires from the study entry to time of MRI.

In addition to age, sex, and race obtained at study entry, other characteristics were also measured, including education, body mass index, smoking status, alcohol consumption, pulmonary function, and prevalent knee osteoarthritis defined as consistent knee pain for at least 1 month in the past 12 months. Pulmonary function was assessed by the ratio of forced expiratory volume in the first second and forced vital capacity.

Statistical Analysis

Univariate associations of PA with MD, fractional anisotropy, parenchyma atrophy, and WM hyperintensities were tested using analysis of variance or χ^2 tests as appropriate. Change in time spent walking was tested using repeated-measures analysis of variance using 10 time points. Associations with neuroimaging markers with p value less than .10 were tested in multivariate regression models with PA as dummy

coded vectors using the sedentary group as referent. Models were adjusted for age, sex, and race that were associated with PA or MRI outcomes and were further adjusted for physical function and chronic diseases at study entry. Models were also adjusted for education because of its known associations with PA and brain health.

The hypothesized moderators, physical function and chronic diseases, were tested using hierarchical multivariate regression models: (i) the moderator (if continuous) was centered on the parent scale, (ii) the interaction term between PA and the moderator was created, and (iii) models were conducted by entering PA and the moderator and then adding the interaction. A significant model change after adding the interaction and the interaction with p value less than .05 indicated a significant moderating effect.

The strength of the associations between PA and neuroimaging markers was tested using forward stepwise analysis with all population characteristics including PA transition using change in time spent walking from study entry to time of MRI or the average time spent walking across 10 years in the model. A p value less than or equal to .10 was used as the criteria for entry into the model and a p value greater than or equal to .05 for removal from the model.

Results

Compared with the parent cohort, the 276 participants in this study were less likely to be sedentary (29). The sedentary group had lower body mass index than the lifestyle active group, and they reported less time spent walking at study entry than the exercise active group. Physical and brain function and chronic diseases at study entry or education did not differ significantly between PA groups (Table 1). There was a significant effect of time on time spent walking

Table 1. Characteristics and Health-Related Conditions Over 9 y by PA

	Total (N = 276)	Sedentary (n = 39, 14.1%)	Lifestyle Active (n = 148, 53.6%)	Exercise Active (n = 89, 32.2%)	p Value
Demographics					
Age (y)	72.9 ± 2.7	73.1 ± 2.9	72.9 ± 2.8	72.7 ± 2.6	.792
Female sex	162 (58.7)	22 (56.4)	94 (63.5)	46 (51.7)	.192
Black race	114 (41.3)	12 (30.8)	67 (45.3)	35 (39.3)	.236
Physical function					
Gait speed (m/s)	1.28 ± 0.24	1.23 ± 0.21	1.27 ± 0.25	1.33 ± 0.24	.065
Change in gait speed (m/s)	−0.27 ± 0.26	−0.30 ± 0.28	−0.27 ± 0.26	−0.26 ± 0.24	.646
Annual % change in gait speed	−2.23 ± 2.06	−2.63 ± 2.52	−2.25 ± 2.03	−2.02 ± 1.87	.299
Chronic disease conditions					
Cardiovascular disease	40 (14.8)	7 (18.4)	20 (14.0)	13 (14.6)	.790
Pulmonary disease	28 (10.2)	6 (15.4)	14 (9.5)	8 (9.0)	.513
Hypertension	107 (38.9)	14 (35.9)	64 (43.5)	29 (32.6)	.226
Diabetes	30 (10.9)	8 (20.5)	14 (9.5)	8 (9.0)	.112
Incident cardiovascular disease	33 (12.6)	2 (5.4)	18 (12.9)	13 (15.3)	.315
Incident stroke	9 (3.3)	0 (0.0)	7 (4.9)	2 (2.3)	.268
Cognitive function					
DSST score (0–90)	42.4 ± 12.7	41.5 ± 13.3	41.8 ± 12.8	43.8 ± 12.4	.437
Change in DSST score	−5.9 ± 10.8	−7.3 ± 10.5	−6.3 ± 10.9	−4.6 ± 10.7	.334
Annual % change in DSST	−.99 ± 6.94	−2.05 ± 3.47	−0.77 ± 9.04	−0.89 ± 2.95	.586
3MSE score (0–100)	92.2 ± 6.3	91.3 ± 6.5	92.7 ± 5.9	91.8 ± 6.8	.310
Change in 3MSE score	0.6 ± 5.8	1.1 ± 6.5	−0.1 ± 5.8	1.5 ± 5.5	.116
Annual % change in 3MSE	0.10 ± 0.73	0.16 ± 0.80	0.01 ± 0.71	0.21 ± 0.72	.113
Depressive symptoms					
CES-D score (0–60)	4.1 ± 4.4	4.6 ± 5.0	4.3 ± 4.4	3.4 ± 4.0	.203
Change in CES-D score	2.9 ± 6.3	4.4 ± 6.0	2.6 ± 6.0	2.7 ± 6.8	.255
Annual % change in CES-D	21.31 ± 45.72	26.32 ± 44.89	19.78 ± 39.21	21.63 ± 55.58	.729
Other characteristics related to PA					
Education > high school	140 (50.9)	14 (35.9)	76 (51.4)	50 (56.8)	.200
Body mass index, kg/m^2	27.4 ± 4.6	25.5 ± 3.6	28.1 ± 4.7	26.9 ± 4.5	.004
Current smokers	13 (4.7)	2 (5.1)	9 (6.1)	2 (2.2)	.649
Alcohol consumption >7 drinks/wk	23 (8.3)	3 (7.7)	15 (10.1)	5 (5.6)	.428
Pulmonary function	77.0 ± 7.4	77.8 ± 9.1	77.2 ± 7.7	76.5 ± 6.3	.603
Knee osteoarthritis	18 (6.5)	1 (2.6)	12 (8.1)	2 (5.6)	.421
Time spent walking (min/wk)					
Time spent walking	60 (225)	20 (135)	40 (143)	190 (385)	.008
Change in time spent walking	−104.3 ± 380.0	−13.0 ± 117.1	−91.5 ± 347.2	−167.6 ± 488.7	.092

Notes: Values are mean ± *SD*, *N* (%), or median (interquartile range). p values were obtained from analysis of variance or χ^2 tests as appropriate. 3MSE = modified mini-mental state examination; CES-D = Center for Epidemiologic Studies Depression Scale; DSST = digit symbol substitution test; PA = physical activity.

across 10 years ($p = .022$). The linear effect of time was also significant ($p < .001$). However, there was no significant interaction between time and PA group ($p = .193$).

Neuroimaging markers from total brain did not differ significantly between groups (Table 2). By contrast, PA was significantly associated with MD in medial temporal lobe and cingulate cortex (Table 3, Model 1). Associations followed a dose–response relationship (linear trend $p = .012$ and .009, respectively). Markers in other regions and tracts did not differ significantly between groups, including striatum, primary sensorimotor cortex, supplementary motor area, and uncinate and superior longitudinal fasciculi (Supplementary Tables 2 and 3).

In multivariate regression models of PA predicting MD in medial temporal lobe, the exercise active group had lower MD than the sedentary group, independent of age, sex, and race (Table 3, Model 2). The association was attenuated after adjustment for diabetes (Table 3, Model 3 vs 2; $\Delta\beta = 11.4\%$) and hypertension (Table 3, Model 4 vs 2; $\Delta\beta = 4.0\%$), but remained significant. The interactions between PA and diabetes or hypertension were not significant ($p > .05$). Adjustment for gait speed, other chronic diseases, or education did not substantially attenuate these associations (all $\Delta\beta < 10\%$). In stepwise analyses, the association remained significant ($\beta = -.407$, $p = .024$) with age, sex, and hypertension retained in the model.

In multivariate regression models of PA predicting MD in cingulate cortex, the exercise active group had lower MD than the sedentary group, independent of age, sex, and race (Table 4, Model 2). The association was attenuated after adjustment for diabetes (Table 4, Model 3 vs 2; $\Delta\beta = 23.3\%$), but remained significant. The interaction of PA and diabetes was not significant ($p = .677$). Adjustment for gait speed, other chronic diseases, or education did not substantially attenuate these associations (all $\Delta\beta < 10\%$). In stepwise analyses, the association remained significant ($\beta = -.381$, $p = .037$) with age, race, diabetes, and DSST score retained in the model.

Table 2. Neuroimaging Markers From Total Brain and Univariate Associations With PA

	Fractional Anisotropy	Mean Diffusivity*	Parenchyma Atrophy, cm^3	White Matter Hyperintensities†
Total ($N = 276$)	0.3581 ± 0.0140	1.3057 ± 0.1102	908.4 ± 137.0	138 (50.0)
Sedentary ($N = 39$, 14.1%)	0.3552 ± 0.0176	1.3326 ± 0.1337	892.3 ± 153.3	22 (56.4)
Lifestyle active ($N = 148$, 53.6%)	0.3581 ± 0.0132	1.3062 ± 0.1105	910.0 ± 129.3	78 (52.7)
Exercise active ($N = 89$, 32.2%)	0.3594 ± 0.0136	1.2930 ± 0.0968	912.6 ± 143.2	38 (42.7)
p value	.298	.174	.726	.226

Notes: Values are mean ± *SD* or *N* (%). *p* values were obtained from analysis of variance or χ^2 tests as appropriate. PA = physical activity.
*Multiplied by 1,000.
†Dichotomized at the median.

Table 3. Regression Models of PA Predicting MD in Medial Temporal Lobe

	Model 1: Unadjusted	Model 2: Adjusted for Age, Sex, and Race	Model 3: Model 2 + Diabetes	Model 4: Model 2 + Hypertension
	β (95% CI), *p*			
Sedentary	Reference	Reference	Reference	Reference
Lifestyle active	−.192 (−0.544, 0.160), .283	−.131 (−0.458, 0.196), .433	−.086 (−0.414, 0.242), .606	−.148 (−0.471, 0.175), .368
Exercise active	−.431 (−0.806, −0.055), .025	−.405 (−0.753, −0.057), .023	−.359 (−0.708, −0.010), .044	−.389 (−0.733, −0.046), .027
Diabetes	—	—	.362 (0.005, 0.718), .047	—
Hypertension	—	—	—	.347 (0.122, 0.572), .003

Note: MD = mean diffusivity; PA = physical activity.

Table 4. Regression Models of PA Predicting MD in Cingulate Cortex

	Model 1: Unadjusted	Model 2: Adjusted for Age, Sex, and Race	Model 3: Model 2 + Diabetes
	β (95% CI), *p*		
Sedentary	Reference	Reference	Reference
Lifestyle active	−.395 (−0.745, −0.044), .028	−.328 (−0.660, 0.004), .053	−.253 (−0.592, 0.086), .131
Exercise active	−.536 (−0.910, −0.162), .005	−.497 (−0.851, −0.144), .006	−.421 (−0.781, −0.061), .019
Diabetes	—	—	.602 (0.234, 0.970), .001

Note: MD = mean diffusivity; PA = physical activity.

When the sedentary group was defined by the amount of lifestyle activities only, associations with MD in medial temporal lobe and cingulate cortex remained similar (β, p values: −.314, .059 and −.506, .006, respectively).

Discussion

In this cohort of adults aged 70–79, a relatively large proportion of participants engaged in lifestyle and exercise activities. Our findings suggest that being exercise active, such as walking for exercise, exercising, or doing recreational activities, for at least 1,000 kcal every week, may be optimal for microstructural integrity in GM among older adults with a range of physical and brain function and chronic diseases.

This study extends prior investigations on the dose–response relationship between PA and brain structure in older adults (11,14). First, the application of high-resolution diffusion tensor imaging allowed the identification of focal associations at the microstructural level. Although previous studies identified the hippocampus as a region related to PA (10,11), these studies relied on low-resolution imaging and volumetric measurements of the brain. Examining specific networks of the microstructure can help understand the mechanisms underlying the neuroprotective effects of PA in old age. Second, this study included a comprehensive characterization of health-related conditions at multiple time points, which could affect PA and were important contributors to brain integrity. Our findings indicate that diabetes may have a moderating effect on the association of PA with microstructural integrity. It has been proposed that PA can protect against cognitive dysfunction and brain neurodegeneration by reducing CVD conditions, including diabetes (34). The moderating effect of diabetes needs to be further explored to formulate individualized prescriptions of PA to promote brain health in older adults.

Contrary to our expectations, we did not find an association of PA with WM integrity. These null findings appeared inconsistent with previous reports. Recent cross-sectional studies indicated that higher PA and fitness were associated with greater WM integrity (14,35), and one intervention study reported increases in fitness from walking was associated with elevated WM integrity in young older adults (18). It is possible that being exercise active may not impact WM integrity a decade later, because the evolution of WM degeneration is stronger for very old adults than for young older adults and it may override the short-term but potentially beneficial effects of PA. It is also possible that the association was not detected due to the small sample.

A strength of this study was the availability of repeated measures of time spent walking to estimate the potential for cross-over between groups (eg, the sedentary may have become exercise active and vice versa). Although less comprehensive than the PA measure that we used as main independent variable, time spent walking has been applied in other investigations (11,12), and it was positively associated with PA type ($p = .008$) in this study. Extreme transitions appeared unlikely in this cohort, because change in time spent walking over time did not significantly differ among three groups as shown in the secondary analysis of existing data. On average, the exercise active group reported more time spent walking than the sedentary group across 10 years ($p < .001$).

Because brain MRI was not obtained at study entry, a possible reverse causality between PA and brain integrity cannot be ruled out. Those with a more favorable neuroimaging profile at study entry could have engaged in higher PA. However, adjustment for cognitive function at study entry, a surrogate marker of brain integrity, did not modify these associations.

One of the limitations is using PA as a categorical variable, which is less sensitive to small variations in PA-related behaviors compared with a continuous variable. We chose this coding because it has been previously validated in the parent cohort (28,29). Furthermore, self-reported PA may be less sensitive in measuring low intensity activities compared with objective measures. For example, the SenseWear Armband is more valid and accurate in detecting low intensity activities than self-report measures. Future neuroimaging studies applying objective measures are warranted to quantify small amounts and small variations of PA. Another methodological limitation is that the presence of crossing fibers may affect the estimate of fractional anisotropy in WM (36). However, our approach is based on predefined anatomic tracts of interest, which is less susceptible to this limitation than tractography. Lastly, this cohort may not well represent the general population of older adults due to voluntary participation and MRI eligibility. While possible, we also noted that our analytic sample and the participants seen in 2006–2008 without a brain MRI shared similar baseline characteristics.

Conclusions

As the number of very old adults rises, so does the incidence of cognitive impairment and dementia. A major public health priority is to identify strategies to prevent or delay the progression of brain abnormalities using effective interventions for older people. This study suggests that being exercise active may help preserve brain microstructural integrity in memory-related networks among community-dwelling older adults. Future studies are warranted to explore the moderating effect of diabetes on the neuroprotective effect of PA.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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