Not Just for Joints: The Associations of Moderate-to-Vigorous Physical Activity and Sedentary Behavior with Brain Cortical Thickness

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ABSTRACT

FALCK, R. S., C. L. HSU, J. R. BEST, L. C. LI, A. R. EGBERT, and T. LIU-AMBROSE. Not Just for Joints: The Associations of Moderate-to-Vigorous Physical Activity and Sedentary Behavior with Brain Cortical Thickness. *Med. Sci. Sports Exerc.*, Vol. 52, No. 10, pp. 2217–2223, 2020. **Introduction:** Cortical thinning is associated with aging; however, lifestyle factors can moderate this relationship. Two distinct lifestyle behaviors associated with brain health are regular moderate-to-vigorous physical activity (MVPA) and limited sedentary behavior (SB). However, it is unclear whether MVPA and SB levels contribute to cortical thickness independent of each other. We therefore investigated the independent relationships of MVPA and SB with cortical thickness using baseline data from a randomized controlled trial. **Methods:** At baseline, we measured MVPA and SB for 7 d using the SenseWear Mini. A subset of the randomized controlled trial participants (n = 30) underwent a 3T magnetic resonance imaging scan, wherein region-specific cortical surface morphometric analyses were performed using T1-weighted structural magnetic resonance imaging. We conducted regression analyses using a surface-based cluster size exclusion method for multiple comparisons within FreeSurfer neuroimaging software to determine if MVPA and SB are independently correlated with region-specific cortical thickness. **Results:** This subset of participants had a mean age of 61 yr (SD = 9 yr), and 80% were female. Higher MVPA was associated with greater cortical thickness in the temporal pole (cluster size, 855 mm^2; cortical thickness range, 2.59–3.72 mm^2; $P < 0.05$) and superior frontal gyrus (cluster size, 1204 mm^2; cortical thickness range, 2.41–3.15 mm^2; $P < 0.05$) of the left hemisphere, independent of SB. Sedentary behavior was not associated with greater cortical thickness in any region, independent of MVPA. **Conclusions:** Our results indicate that adults with greater MVPA—independent of SB—are associated with greater cortical thickness in regions, which are susceptible to age-associated atrophy. **Key Words:** PHYSICAL ACTIVITY, SEDENTARY BEHAVIOR, OLDER ADULTS, BRAIN

Aging is characterized by multifaceted changes in brain structure and brain function, resulting in age-related changes in cognitive performance related to memory, processing speed, reasoning, and executive functions (1). Cortical thinning is also a hallmark of the aging process, beginning in as early as middle adulthood and particularly affecting the prefrontal cortex and the medial temporal lobe (2). However, declining brain health with increasing age is not inevitable because lifestyle modifications can alter the course of brain aging (3).

Cortical thickness is an integral aspect of cognitive health throughout life (4), and better brain health in later life is linked to the maintenance of cortical thickness as adults age (5). Older adults with mild cognitive impairment have less cortical thickness than healthy older adults, whereas older adults with Alzheimer's disease have less cortical thickness than older adults with mild cognitive impairment—suggesting that there may be a progression of cortical thinning which occurs as cognitive health worsens (6). Cortical thinning in the temporal and parietal lobes also predicts conversion from prodromal to mild Alzheimer's disease (7), and thinning in vulnerable cortical regions relates to Alzheimer's disease symptom severity—even in the earliest stages of the disease (8). Cortical thinning is also associated with disruption of cortical–white matter networks in people with dementia (9), further suggesting that the preservation of cortical thickness may be integral to healthy brain aging.

Two lifestyle factors associated with better brain and cognitive health are regular moderate-to-vigorous physical activity

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(MVPA) and limited sedentary behavior (SB) (10). Briefly, MVPA is any bodily movement which incurs ≥3.0 metabolic equivalents (METs), whereas SB refers to any waking behavior which incurs ≤1.5 METs and occurs while sitting or lying down. Meeting the current guidelines of ≥150 min·wk^{-1} of MVPA reduces the risk of Alzheimer's disease by up to 38% (11), and an estimated 18% of all Alzheimer's disease cases could be prevented by all adults meeting these guidelines (12). Too much SB can also negatively impact brain health by reducing glycemic control (13), which lead to brain atrophy, white matter hyperintensities and cerebral infarcts (14). Importantly, it is critical to examine the role of both MVPA and SB concomitantly because low MVPA and high SB are each distinct risk factors for cognitive impairment (10).

Moderate-to-vigorous physical activity is associated with greater total gray matter volume (15) and reduced age-associated atrophy in the frontal and temporal lobes (16). This may be especially critical because cortical thinning in the frontal and temporal lobes is linked to cognitive impairment and dementia (8). Compared with MVPA, there are few studies which have examined the association between SB and neuroimaging outcomes. However, it has been hypothesized that SB may impact brain and cognitive health by either 1) the inverse of MVPA mechanisms, which promote brain and cognitive health; or 2) by compromising glycemic control, which can alter cerebral blood flow and potentially lead to cortical atrophy (10). One study found that self-reported SB is associated with reduced cortical thickness in the medial temporal lobe (17); however, no study has yet examined whether objectively measured SB is associated with cortical thickness, and few studies have examined whether objectively measured MVPA is associated with better brain health. As we have highlighted previously (18), self-reported levels of MVPA and SB are likely biased. Self-report is vulnerable to recall bias because MVPA participation among older adults is often intermittent, sporadic, or unstructured, which makes recall extremely difficult and may lead to unintentionally overreporting or underreporting MVPA and SB. Furthermore, it is currently unclear whether MVPA is associated with cortical thickness independent of SB or *vice versa*. Determining whether each of these behaviors is independently associated with cortical thickness could help refine the public health message for healthy brain aging.

To address these knowledge gaps, we investigated the independent relationships of objectively measured MVPA and SB with cortical thickness. Based on the current evidence of how MVPA and SB are associated with brain health, we expected greater MVPA to be associated with greater cortical thickness in the temporal and frontal lobes, whereas SB would be associated with less cortical thickness in the temporal lobe.

METHODS

Study Design

This was a cross-sectional secondary analysis of baseline data from *Monitor-OA*, a 6-month proof-of-concept randomized controlled trial examining the efficacy of a technology-enabled counseling intervention for increasing MVPA and reducing SB in adults with knee osteoarthritis (19). The study occurred between November 1, 2015, and June 1, 2017. The research protocol was approved by the University of British

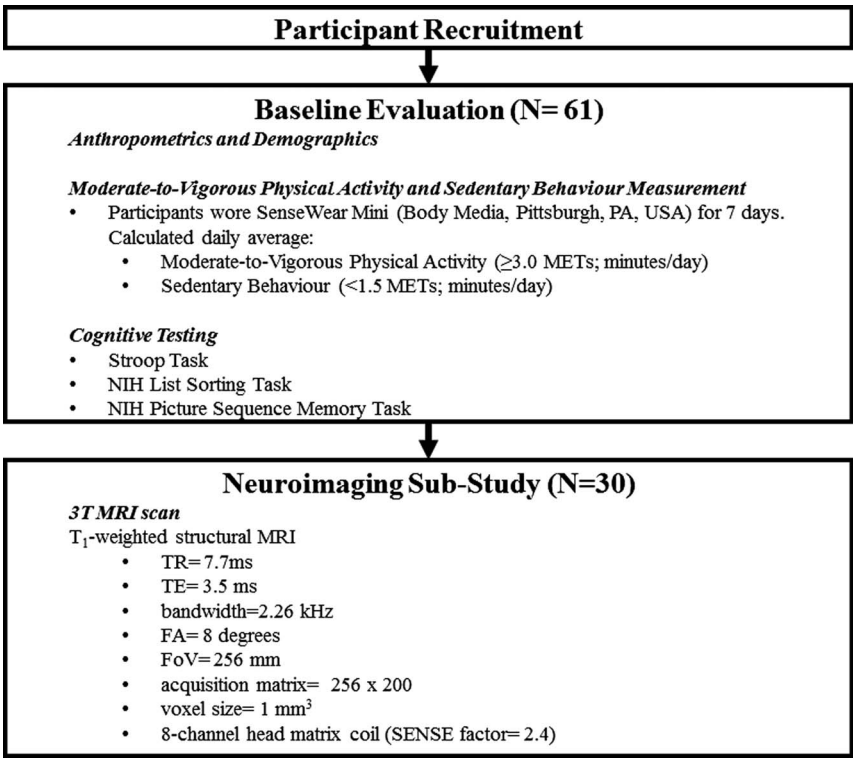

FIGURE 1—STROBE diagram.

Columbia Behavioral Research Ethics Board (application number: H14-01762) and was published on ClinicalTrials.gov (NCT02315664). All participants provided written informed consent.

Figure 1 describes the study design. At study entry, all participants ($n = 61$) underwent a baseline evaluation wherein we measured anthropometrics and demographics, observed MVPA and SB for a period of 7 d, and then performed cognitive testing after this observation period. Before the start of the intervention, we recruited a subsample of 30 participants for our neuroimaging substudy, wherein all participants underwent magnetic resonance imaging (MRI) scanning.

Participants

Details of our specific inclusion and exclusion criteria can be found elsewhere (19). Briefly, we recruited individuals who had a physician confirmed diagnosis of knee osteoarthritis, or passed two criteria for early osteoarthritis: 1) 50 yr and older; and 2) had experienced pain or discomfort in or around the knee lasting >28 consecutive or separate days within the last 12 months (20). We excluded individuals for the following reasons: 1) were diagnosed with inflammatory arthritis, connective tissue diseases, fibromyalgia, or gout; 2) were using disease modifying antirheumatic drugs or gout medications; 3) were planning to receive a total knee arthroplasty or had received a knee arthroplasty; 4) had an acute knee injury or received hyaluronate injections or a steroid injection in the last 6 months; 5) did not have an email address or daily access to a personal computer with Internet access; 6) had a body mass index (BMI) of >40 $kg \cdot m^{-2}$; 7) had received a steroid injection in the last 6 months; 8) were using medications that impaired activity tolerance (such as beta-blockers); or 9) had an inappropriate level of risk for increasing their unsupervised physical activity. Potential participants completed the Physical Activity Readiness Questionnaire (21). If a potential risk was identified by the Physical Activity Readiness Questionnaire, physician confirmation was required to ensure the participant was able to be physically active without the direct supervision of a health professional.

Measures

Demographics and anthropometrics. At baseline, we obtained general health history and demographics information by questionnaire. Height and body weight were ascertained using a calibrated stadiometer and an electronic scale, respectively. Body mass index ($kg \cdot m^{-2}$) was calculated, and global cognitive function was assessed by both the Mini-Mental State Examination (22) and the Montreal Cognitive Assessment (23). In addition, we queried for knee osteoarthritis severity using the Knee Injury and Osteoarthritis Outcome Score (KOOS) (24). The KOOS is a patient self-reported outcome instrument which assesses an individual's opinion about their knee osteoarthritis. The KOOS contains 42 items across five separate scored subscales: pain, symptoms, activities of daily living, and quality of life.

MVPA and SB. We measured MVPA and SB using the SenseWear Mini (Body Media, Pittsburgh, PA), a multisensor monitor that is worn on the upper arm over the triceps (25). The device integrates triaxial accelerometer data, physiological sensor data, and personal demographic information to provide valid and reliable estimates of MVPA and SB (25,26). Participants wore the device on the nondominant arm for 7 d at each assessment. We reduced data to average minutes per day of MVPA (≥3.0 METs) and minutes per day of SB (≤1.5 METs).

MRI Data Acquisition and FreeSurfer Analyses

The MRI data acquisition was conducted at the University of British Columbia MRI Research Centre using a Philips Achieva 3.0 Tesla MRI scanner with an eight-channel sensitivity encoding neurovascular coil (SENSE factor = 2.4). High-resolution T1 images were obtained with the following parameters: 1) slice thickness of 1 mm^3; 2) repetition time of 7.7 ms; 3) echo time of 3.5 ms; 4) bandwidth of 2.26 kHz; 5) flip angle of 8°; 6) field of view 256 mm; and 7) acquisition matrix size of 256 × 200.

We used the FreeSurfer version 6.0 image analysis suite, developed at the Martinos Centre for Biomedical Imaging by the Laboratory for Computational Neuroimaging (http://surfer.nmr.mgh.harvard.edu/), to calculate cortical thickness. FreeSurfer consists of two processing streams, a surface-based stream and a volume-based stream. The surface-based stream constructs models of the white matter–gray matter boundary and the boundary between the gray matter and cerebrospinal fluid (i.e., pial surface) from which cortical thickness is estimated as the shortest distance between the two. Cortical labeling is based on a subject-independent atlas (i.e., the Talairach space) and the subject-specific values. These labels are then morphed onto a common space (cohort mean) to achieve a common point of reference for each subject relative to the clinical population studied. This coordinate system can be subsequently used to examine associations of cortical thickness with variables of interest (27).

We performed our FreeSurfer analyses (see Appendix, Supplemental Digital Content, FreeSurfer Imaging Analysis Procedure, http://links.lww.com/MSS/B977) using a recent investigation as a guide (28). Data processing included skull stripping (29), motion correction (30), Talairach transformation (31), and atlas registration (32). After surface reconstruction and segmentation, the resulting output was visually inspected for quality and accuracy by R. S. F., C. L. H., and J. R. B. Automated skull stripping inaccuracies were manually corrected, intensity normalization failures (requiring the addition of white matter control points), incorrect white matter segmentation, automated topological fixer errors, and pial surface inaccuracies. The *recon-all* processing stream was then re-run using the *recon-all-qcache* flag to resample the data onto the FreeSurfer *fsaverage* (cohort mean subject) and smooth the images with a 10-mm full-width at half-maximum Gaussian Kernel.

General Linear Model analyses were then performed to assess the independent associations of MVPA and SB with

TABLE 1. Participant characteristics.

Participant Characteristics	All Participants ($N = 61$)	MRI Participants ($n = 30$)	Non-MRI Participants ($n = 31$)	P*
Age (yr)	62 (9)	61 (9)	63 (8)	0.36
%Female	0.82	0.8	0.84	0.95
BMI (kg·m^{-2})	29.20 (5.10)	29.82 (4.85)	28.61 (5.34)	0.36
Education				
High school degree or less	18%	20%	16%	0.36
Some university	31%	20%	42%	
University degree or higher	51%	60%	42%	
KOOS[a]				
Pain	65.6 (17.6)	65.7 (17.9)	65.5 (17.5)	0.96
Symptoms	61.6 (16.5)	64.2 (15.3)	60.1 (16.9)	0.33
Activities of daily living	73.2 (17.4)	74.0 (17.2)	73.3 (17.4)	0.88
Sport and recreation	50.7 (27.4)	51.3 (25.9)	51.3 (28.8)	0.99
Quality of life	43.1 (18.1)	44.0 (15.7)	42.9 (20.3)	0.83
MVPA (min·d^{-1})	85 (74)	70 (48)	99 (91)	0.12
SB (min·d^{-1})	693 (138)	698 (118)	688 (157)	0.77
Total brain volume (mm^3)	—	1,063,234 (95,729)	—	—
Total gray matter volume (mm^3)	—	589,401 (50,900)	—	—
Total cerebral white matter volume (mm^3)	—	446,701 (48,546)	—	—
Whole brain average cortical thickness (mm^2)	—	2.43 (0.08)	—	—

Mean (SD) or %.
* P values from independent samples t tests and x^2 tests for differences between MRI participants and non-MRI participants.
[a]All subscales are scored out of 100, with lower scores indicating greater severity.

cortical thickness by implementing the mri_glmfit script using 1) *DOSS* (different offset, same slope) as a design matrix; 2) MVPA and SB as independent variables of interest; and 3) age, sex, and education as covariates. We then corrected for multiple comparisons using a cluster-wise correction method (33). Vertex-wise analyses were corrected for multiple comparisons using the *mri_glmfit-sim* toolbox in FreeSurfer, with a cluster forming threshold of 1.3 (i.e., $P < 0.05$) and cluster-wise probability set to $P < 0.05$. P values were adjusted for both hemispheres to correct for the full search space. This was repeated for 10,000 iterations to derive the location of cluster sizes under the null hypothesis. Clusters surviving cluster-wise correction were then superimposed on *fsaverage* inflated surfaces using *tksurfer*, a GUI application available in FreeSurfer. We then performed a subsequent analysis wherein we accounted for osteoarthritis symptom severity by including the KOOS Pain Subscale as an additional covariate (24).

RESULTS

Participant characteristics. Participant characteristics are described in Table 1. There were no significant differences in any descriptive variables between participants included in this substudy ($n = 30$) and those from the full sample who were not included ($n = 31$).

For participants included, mean participant age was 61 yr (SD = 9 yr), 80% of the sample was female, and average BMI was 29.82 kg·m^{-2} (SD = 4.85 kg·m^{-2}). Participants reported moderate pain (KOOS pain = 65.7; SD = 17.9) and moderate symptoms (KOOS symptoms = 64.2; SD = 15.3). Participants engaged in 70 min·d^{-1} (SD = 48 min·d^{-1}) and 698 min·d^{-1} (SD = 118 min·d^{-1}) of MVPA and SB, respectively. Average total brain volume was 1,063,234 mm^3 (SD = 95,729 mm^3), and average cortical thickness was 2.43 mm^2 (SD = 0.08 mm^2).

Independent relationships of MVPA and SB with cortical thickness. We identified two significant clusters which survived cluster-wise correction in the left superior frontal gyrus (cluster size, 1204 mm^2; cortical thickness range, 2.41–3.15 mm^2; $P < 0.05$) and in the temporal pole (cluster size, 855 mm^2; cortical thickness range, 2.59–3.72 mm^2; $P < 0.05$), where participants who engaged in greater amounts of MVPA showed greater cortical thickness in these regions independent of time spent in SB (Fig. 2). No clusters survived correction when examining the relationship between SB and cortical thickness.

Our subsequent analysis, wherein we included KOOS pain score as a covariate, is described in Figure 3. Two significant clusters survived cluster-wise correction; one in the left superior frontal gyrus (cluster size, 1229 mm^2; cortical thickness range, 2.41–3.15 mm^2; $P < 0.05$) and another in the right frontal pole (cluster size, 786 mm^2; cortical thickness range, 2.08–2.87 mm^2; $P < 0.05$). No clusters survived correction for the relationship between SB and cortical thickness.

DISCUSSION

Our results suggest that MVPA, but not SB, is associated with greater cortical thickness in the left hemisphere regions of the superior frontal gyrus and the temporal pole in community-dwelling older adults. When we accounted for osteoarthritis symptom severity, our results indicated that MVPA was still associated with greater cortical thickness in the left superior frontal gyrus, as well as in the right frontal pole. Cortical thinning of the frontal and temporal lobes are each associated with aging and dementia (2–8), and thus engaging in regular MVPA is integral for maintaining brain health in older adulthood.

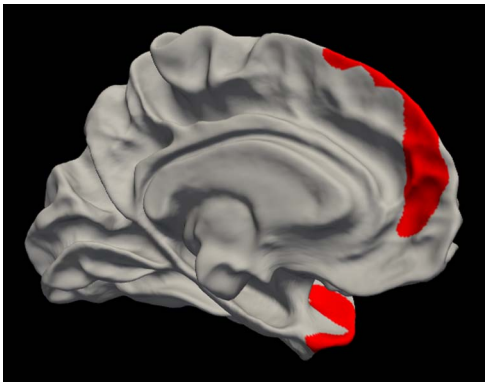

FIGURE 2—Significant multiple comparison corrected clusters of greater cortical thickness associated with higher MVPA independent of SB. Higher MVPA is associated with greater cortical thickness in the temporal pole and the superior frontal gyrus of the left hemisphere. Model accounting for age, sex, and education.

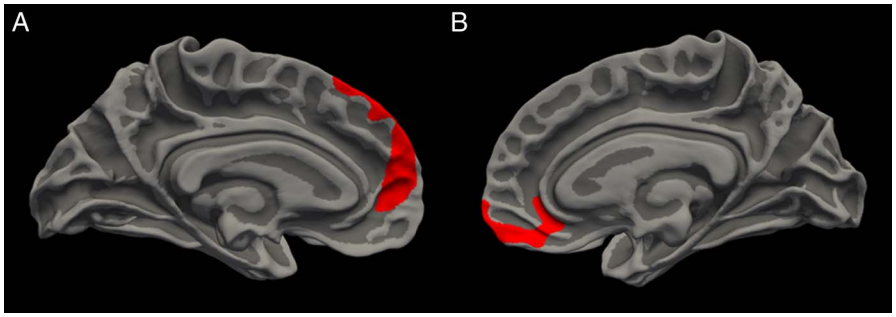

FIGURE 3—Significant multiple comparison corrected clusters of greater cortical thickness associated with higher MVPA independent of SB. Higher MVPA is associated with greater cortical thickness in the (A) left superior frontal gyrus; and (B) right frontal pole. Model accounting for age, sex, education, and osteoarthritis severity using the KOOS Pain Subscale.

Contrary to our hypothesis, our results do not indicate that greater amounts of SB are associated with less cortical thickness independent of MVPA. Only one study, to date, has examined the relationship between SB and brain health (17). The authors found that higher amounts of self-reported SB were associated with decreased medial temporal lobe thickness; however, our results do not indicate that SB is associated with brain structure independent of MVPA. One potential explanation is that higher amounts of MVPA provide a strong neuroprotective response which ameliorates the negative consequences of too much SB. Indeed, our sample was both highly active and highly sedentary, engaging in an average of 70 min·d^{-1} of MVPA and nearly 12 h·d^{-1} of SB. It is, thus, plausible that the pejorative cellular consequences of too much SB affects the same pathways by which MVPA improves brain health (10). Although engaging in high amounts of SB appears to have deleterious effects on glucose tolerance, which appears to be critical for maintaining brain health (13,14), even single bouts of MVPA in the form of exercise can have dramatic effects on glucose tolerance (34). Moderate-to-vigorous physical activity in the form of exercise training improves glycemic control, with the most substantial evidence coming from studies of people with type 2 diabetes mellitus (35), who are often more sedentary than their healthy peers (36). Moreover, MVPA in the form of exercise training in adults with impaired glycemic control improves insulin sensitivity and cognitive function (37), further implicating that high amounts of MVPA may shield the brain from the consequences of high SB on brain health.

Although our study appears to further support evidence that high MVPA mollifies some of the negative consequences of SB on brain health, the science is far from settled. Epidemiological data points to high SB being a risk factor for metabolic disease independent of MVPA (13), and there is at least some indication that SB is associated with poorer cognitive health independent of MVPA (10). Moreover, there is a growing body of evidence which suggests that higher amounts of light physical activity (i.e., 1.5–3.0 METs), such as household chores, may also help maintain brain health (38). Although our exploratory investigation cannot definitively determine which of these behaviors is most critical to promoting better brain health, our results indicate that higher MVPA is critical to maintaining cortical thickness in areas associated with cognitive decline independent of SB (6–8). Based on the current results, and keeping with the current guidelines for healthy cognitive aging (10), we strongly recommend that all adults 1) engage in ≥150 min·wk^{-1} of MVPA; and 2) limit discretionary SB to <2 h·d^{-1}.

Limitations. There are a number of study limitations, most importantly our cross-sectional design such that no causal effects can be elucidated. Our sample was composed of adults with knee osteoarthritis, and thus our results may not generalize to those without knee osteoarthritis. However, osteoarthritis is a common condition in later life with 9% of all men and 18% of all women older than 60 yr have osteoarthritis (39). Our sample size did not allow us to adequately examine whether brain regions which were associated with MVPA were also associated with cognitive function, and thus we cannot assess whether cortical thinning in the superior frontal region and the temporal pole are also associated with poorer cognitive performance (10). Our sample was also highly active in comparison to the general population. Less than 95% of adults meet the current MVPA guidelines of 150 min·wk^{-1} of activity (40); however, most of our sample well exceeded these guidelines. We also did not examine whether MVPA moderated the relationship of SB with cortical thickness, or *vice-versa*. Such an investigation appears warranted, however, given that our results appear to indicate that MVPA may attenuate the negative consequences of SB on the brain. Unfortunately, our sample size is too small to perform such an analysis, and thus future studies are needed to examine the interaction of MVPA and SB with brain structure.

Lastly, we did not measure cardiovascular fitness, and thus cannot determine whether fitness or MVPA and SB levels are more important for older adult brain health. Investigations into how MVPA and SB are associated with brain health have traditionally used cardiovascular fitness as a proxy or endpoint of activity level (15). Although these studies have consistently found an association between cardiovascular fitness and better brain structure, there is a debate whether cardiovascular fitness is directly linked to MVPA level (41). Future research is, thus, needed to determine whether fitness or activity level is more important for brain health.

CONCLUSIONS

In summary, higher MVPA is associated with greater cortical thickness in the superior frontal gyrus and the temporal pole, independent of SB level. Our results help refine the current healthy cognitive aging guidelines on MVPA and SB by indicating that MVPA maintains cortical structure in later life independent of SB level (10). Encouraging all adults to meet MVPA guidelines may therefore help maintain the brain health of the population. Future research should examine how MVPA level, independent of cardiovascular fitness, is associated with cortical thickness.

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R. S. F. wrote the first draft of the article. R. S. F., J. R. B., and T. L. A. conceived the study concept and design. R.S.F. and J.R.B. collected the data. R. S. F., C. L. H., and A.R.E. performed the data analysis and interpreted the results. C. L. H., J. R. B., L. C. L., A. R. E., and T.L. A. wrote portions of the article and provided critical review. All authors have read and approve of the final article.

The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM.

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