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Lifetime Physical Activity and White Matter Hyperintensities in Cognitively-Intact Adults

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Abstract

Background: White matter hyperintensities (WMH) observed on magnetic resonance images are associated with depression and increase risk of stroke, dementia and death. The association between physical activity and WMH has been inconsistently reported in the literature, perhaps because studies did not account for a lifetime of physical activity or depression.

Objectives: To determine the extent to which a lifetime of leisure-time physical activity is associated with less WMH while accounting for depression.

Methods: Face-to-face interviews were conducted with the Lifetime Total Physical Activity Questionnaire where the metabolic equivalent of task (MET) hours per week per year was calculated. Cognitively-intact participants also underwent magnetic resonance imaging where WMH as a percentage of intracranial volume (ICV) was obtained. Hierarchical multiple linear regression was performed to compare WMH in a more active group with no psychiatric history ($n = 20$, $\bar{x}$ age = 62.2) with a less active group with no psychiatric history ($n = 13$, $\bar{x}$ age = 64.0) and a less active group with history of late-onset depression ($n = 14$, $\bar{x}$ age = 62.8).

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Results: There was not a statistically significant difference in WMH_{lg10} between the more and less active groups without a psychiatric history ($b = .09, p > .05$), or between the more active group without a psychiatric history and the less active group with a history of depression ($b = .01, p > .05$). The model was predictive of WMH_{lg10}, explaining an adjusted 15% of the variance in WMH ($p = .041$).

Discussion: A lifetime of leisure-time physical activity was not associated with WMH when accounting for depression.

Keywords

aging; exercise; brain; depression; leukoaraiosis

White matter hyperintensities (WMH) are patchy areas of hyperintense signals scattered in the white matter of the brain evident on magnetic resonance images (Moroni, Ammirati, Rocca, Filippi, Magnoni, & Camici, 2018). WMH are common with aging, have been associated with several neuropsychiatric disorders including depression (Herrmann, Le Masurier, & Ebmeier, 2008), and increase the risk of stroke, dementia and death (Moroni et al., 2018). Physical activity has been shown to reverse WMH in cognitively impaired individuals (Suo et al., 2016) and slow the age-related progression of WMH in adults with medical co-morbidities (Espeland et al., 2016). However, the effect of physical activity on WMH in cognitively-intact adults with few medical co-morbidities is inconsistent.

A systematic review of the association between physical activity and WMH across longitudinal and cross-sectional studies showed conflicting results (Torres, Strack, Fernandez, Tumey, & Hitchcock, 2015). Physical activity was often associated with less WMH (Booth et al., 2014; Boots et al., 2014; Gow et al., 2012; Saczynski et al., 2008; Sen et al., 2012; Tseng et al., 2013), although several studies were unable to find this association (Carmelli et al., 1999; Ho et al., 2011; Podewils et al., 2007; Rosano et al., 2010; Rovio et al., 2010; Smith et al., 2009; Willey et al., 2011; Zheng et al., 2012). Conflicting results may be due to the time frame of physical activity measurement in relation to the time of WMH measurement (Torres et al., 2015). WMH likely develops over the span of decades. Therefore, to be effective, preventive interventions should begin decades before the onset of illness. For instance, Alzheimer's disease research has provided evidence that interventions designed to prevent or halt symptoms may be most effective when administered in the preclinical stage, which may occur 25 years before the onset of symptoms (Bateman et al., 2012). Few studies have examined the association between physical activity spanning decades and WMH before the onset of symptoms. Rovio et al. (2010) and Carmelli et al. (1999) measured physical activity 21 and 25 years before measurement of WMH, respectively. Yet neither of them found a significant association between physical activity and WMH. Rovio et al. combined individuals who were cognitively intact with those who had mild cognitive impairment and dementia. Carmelli et al. did not report excluding individuals with cognitive impairment or dementia. Neither Rovio et al. or Carmelli et al. reported excluding individuals with depression. The purpose of this study was to determine if a lifetime of physical activity was associated with WMH while accounting for depression in cognitively-intact adults.

Method

Participants

Adults aged 50 or greater were recruited from two sources. One source was a study designed to examine older adults with and without a history of depression and no other psychiatric history (Paradiso, Naridze, & Holm-Brown, 2012). Because a study using the same lifetime physical activity questionnaire used in the present study (described below) found that 96–98% of lifetime physical activity was light-moderate among adults aged 50–65 (Cust et al., 2008), it was expected that the majority of participants would report a lifetime of light-moderate physical activity. Individuals were sent an IRB approved letter about the current study, with the principal investigator's contact information. Out of 18 individuals without a psychiatric history, 15 consented to the current study. Among them, 2 did not have fluid attenuation inversion recovery sequences (FLAIR) images which were required to calculate the WMH, resulting in 13 participants without a psychiatric history in the current study. Thirty-four individuals reported their first episode with depression when they were age 50 or over (i.e. late-onset depression) and no other psychiatric history; out of the 34 individuals, four did not have FLAIR images required to calculate WMHs. Out of the remaining 30 individuals, 15 consented to the current study, of which one had non-usable images, resulting in 14 participants with a history of late-onset depression and no other psychiatric history in the current study.

The second source of recruitment targeted adults in the community expected to report a lifetime of more vigorous leisure-time physical activity. The second source of recruitment came from public websites with results of individuals who completed a regional marathon or half-marathon in the previous year. The websites listed individuals' names, age and the town they lived in. Individuals who lived in the area were sent an IRB approved letter about the current study, with the principal investigator's contact information. The individuals who called were screened over the phone with the Rapid Assessment of Physical Activity among Older Adults (Topolski et al., 2006); inclusion criteria were participation in 20 or more minutes/day of vigorous physical activity 3 or more days/week during the year preceding the interview. This brief validated instrument for clinical practice assesses levels of physical activity among adults aged 50+ (Topolski et al., 2006). A total of 30 individuals were screened for the vigorous physical activity group. Excluded individuals comprised nine with a psychiatric history and one who was much older than the other participants (82, or 2.46 SD above the mean), resulting in 20 vigorously active participants.

Inclusion criteria required all participants to have no obvious cognitive impairment as assessed by the Mini-Mental Status Exam, a validated instrument measuring memory, attention, orientation, language, and praxis (Lin, O'Connor, Rossom, Perdue, & Eckstrom, 2013). Scores range from 0 to 30, with lower scores indicating greater cognitive impairment (Lin et al.). This instrument was administered from an approved copy (Crum, Anthony, Bassett, & Folstein, 1993). The cut-point of 24 has a sensitivity of 88.3% and a specificity of 86.2% to detect increased odds of dementia (Lin et al.).

Exclusion criteria were 1) all contraindications to MRI (including non-removable metallic/electronic implants or reported claustrophobia), 2) inability to answer questions in English,

and 3) medical illness with potential for major repercussion on cognitive status (e.g. seizures, demyelinating disorder, stroke, head injury with loss of consciousness >5 minutes). Two groups could not have a history of any psychiatric disorder, while the group with a history of late-onset depression could not have a history of any other psychiatric disorder. History of psychiatric disorders were assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 4th edition Text Revision Axis I Disorders Research version Non-patient Edition (First, Spitzer, Miriam, & Williams, 2002). Institutional Review Board approval was obtained from the University of Iowa. Informed consent was obtained from all participants.

Physical Activity

Face-to-face interviews were conducted using the Lifetime Total Physical Activity Questionnaire (LTPAQ). The LTPAQ has been used with health issues related to insufficient physical activity across the lifespan such as breast (Friedenreich et al., 2001 & 2009; Tam et al., 2014), endometrial (Friedenreich et al., 2010 & 2011), and prostate cancer (Friedenreich et al., 2004), as well as cognitive function (Gill et al., 2015) and general health outcomes (Boisvert-Vigneault et al., 2016). The LTPAQ assesses four domains of physical activity; leisure-time, occupation, transportation and household plus total (sum of leisure-time, occupation, transportation and household) (Friedenreich, Courneya, & Bryant, 1998) from the start of primary education up to the day of the interview with the LTPAQ (Torres, 2018). Evidence of construct validity was found in the face-to-face administered LTPAQ by comparing physical activity in the current sample with nationally representative samples of self-report and objective assessments of physical activity (Torres, 2018); 1) participants reported more moderate than vigorous physical activity, and 2) the majority of moderate and vigorous physical activity occurred during occupation and household activities followed by leisure-time and then transportation physical activity, providing evidence of construct validity for moderate and vigorous physical activity in all the domains. No evidence of construct validity was provided for sedentary or light physical activity; in contrast to nationally representative samples, participants did not report more sedentary than light, or more light than moderate physical activity. Thus, sedentary and light was omitted from current analyses. The reliability of the face-to-face administered LTPAQ was estimated between two interviews seven weeks apart (Friedenreich et al., 1998): The test-retest correlations for hours per week spent in lifetime occupational and transportation activity was .87, household activity .77, leisure-time .72, and total lifetime physical activity .74.

A recall calendar specifically designed to be used with the LTPAQ was mailed to the participants to complete before the interview (Friedenreich et al., 1998). The recall calendar focused on major life events; medical and reproductive history; education, job and volunteer history, and physical activity. The completed calendar was used during the interview as a memory aid to improve recall. The interviewer was trained in the lab of Dr. Friedenreich, the creator of this questionnaire (Friedenreich et al., 1998), to use cognitive interviewing methods to improve the participants' ability to report their past activity patterns, specifically 1) participants thought aloud when answering the questions, and responses were probed extensively; 2) participants repeated the question in their own words, thereby permitting the interviewer to assess whether they understood the question; 3) the interviewer used follow-

up questions to gain more information about the participants' strategies used for answering questions; and 4) the interviewer used the recall calendar to aid the respondents in recalling past activities.

The patterns of physical activity recorded by the interviewer included the 1) age of the individual when the physical activity started, 2) age of the individual when the physical activity ended, 3) number of hours per day spent on the physical activity, 3) number of days per week spent on the physical activity, 4) number of weeks per year spent on the physical activity, and 5) number of years spent in each activity from the start of primary education up to the time they received their MRI. Each activity was averaged within their respective domain and subsequently converted into energy expended by multiplying the hours spent by the estimated metabolic equivalent of task (MET) of that activity abstracted from the *Compendium of Physical Activities* (Ainsworth et al., 2011). A MET value is the ratio of the metabolic rate for an activity to the resting metabolic rate. One MET is the average seated resting energy cost of an adult, 3.5 mL/kg/min of oxygen. Moderate-intensity is characterized as 3.0–5.9 METs and vigorous-intensity as ≥ 6 METs (Ainsworth et al.). The average MET-hours per week per year for each activity within each domain of physical activity was totaled, divided by the number of years from the start of primary education up to the time they received their MRI, and divided by 48 weeks in a year to come up with the average MET-hours/week/year across the lifespan. Investigators who performed the physical activity calculations did not have access to the WMH volumes.

Brain Imaging Acquisition

Participants underwent magnetic resonance imaging (MRI) on a Siemens TIM Trio 3T scanner using a 12-channel head coil. The acquisition included 3D T1-weighted 1 mm isotropic T1, T2, and T2FLAIR 1. The T1 weighted images were collected using a coronal MP-RAGE sequence (TI=909ms, TE=2.8ms, TR=2350ms, flip angle=10°, field of view=256×256×220mm, matrix=256×256×220, bandwidth=180Hz/pixel, parallel imaging factor=2). The T2 weighted images were collected in the sagittal plane using a 3D SPACE sequence (TE=406ms, TR=4000ms, field of view=260×228×176, matrix=260×228×176, bandwidth=590Hz/pixel, turbo factor=121, parallel factor=2). The T2FLAIR images were collected in the sagittal plane (TI=1800ms, TE=406ms, TR=5000ms, field of view=260×228×176, matrix=260×228×176, bandwidth=592Hz/pixel, turbo factor=121, parallel factor=2).

Intracranial Volume Calculation and WMH Segmentation

Intracranial volume (ICV) was calculated using a “reverse brain masking” method (Keihaninejad et al., 2010) to scale for differences in head size. An ICV probability map is created for each participant by summing gray matter, white matter, and cerebrospinal fluid (CSF) probability maps and applying the inverse deformation field produced from each subject's normalization to produce an ICV mask in native space. A threshold of 0.9 was applied to participant specific ICV probability maps to exclude voxels with less than a 90% probability of being in the brain.

Total volume of WMH was calculated using the open source toolbox Lesion Segmentation Tool version 1.2.2 in SPM8 (Schmidt et al., 2012). Briefly, lesions are seeded based on spatial and intensity probabilities from T1 images and hyperintense outliers on T2 FLAIR images. A binary conservation lesion belief map was created, with an initial threshold of 0.30 from gray and white matter lesion belief maps. A growth algorithm was then applied to create a liberal lesion belief map and a threshold of 1.00 was implemented to remove voxels that had a lower probability of being a lesion (Birdsill et al., 2014). To examine total WMH, WMH volume was divided by ICV and multiplied by 100 to give a white matter hyperintensity ratio in units of percentage of ICV.

Statistical Analyses

Descriptive statistics were performed. The Kruskal-Wallis test was performed to determine if differences between the three groups were statistically significant for age, leisure-time, occupation, transportation, household, and total (sum of leisure-time, occupation, transportation and household) physical activity, MMSE, and WMH. Statistically significant results were followed up with the Dunn procedure to determine group differences. Chi-Square was calculated to determine if differences between the two physical activity groups were statistically significant for demographic and co-morbidities commonly associated with WMH; sex, education, hypertension, coronary heart disease, left ventricular hypertrophy, congestive heart failure, atrial fibrillation, diabetes and dyslipidemia. Multiple linear regression was performed in the more active group without a psychiatric history as the reference group (Polit, 2010). In the first step of the analysis, the association between physical activity and WMH was compared in the more active group without a psychiatric history to the less active group without a psychiatric history while controlling for common predictors of WMH. In the second step of the analysis, the association between physical activity and WMH was compared in the more active group without a psychiatric history to 1) the less active group without a psychiatric history and 2) the less active group with a history of depression while controlling for common predictors of WMH. Univariate analyses conducted in SPSS version 24 (Chicago, IL, USA) were considered significant at $p < 0.05$.

Results

There were no statistically significant differences between the three groups in terms of factors known to be associated with WMH including age, sex, education, Mini-Mental Status Exam, and history of hypertension, coronary heart disease, diabetes and dyslipidemia (see Table 1). None of the participants reported left ventricular hypertrophy, congestive heart failure and atrial fibrillation. There were no statistically significant differences between the three groups in terms of occupation, transportation or household physical activity.

There was a statistically significant difference in leisure-time physical activity across the groups ($H = 6.6$, $p = .036$). Post hoc analysis revealed the physically active group without a psychiatric history reported more leisure-time physical activity than the group with no psychiatric history (median = 23.01 vs. 13.92 respectively, $U = -1.7$, $p = .097$) and the group with a history of late-onset depression (median = 23.01 vs. 12.08 respectively, $U = -2.4$, $p = .017$), although the former was not statistically significant.

There was a statistically significant difference in WMH across the groups ($H = 7.7$, $p = .021$). Post hoc analysis revealed the physically active group reported significantly less WMH than the group with no psychiatric history (median = 1.76 vs. 2.89 respectively, $U = -2.7$, $p = .007$), but not the group with a history of late-onset depression (median = 1.76 vs. 2.00 respectively, $U = -1.3$, $p = .184$).

For multivariate analyses, since there was a statistically significant difference in leisure-time physical activity across all groups ($H = 6.6$, $p = .036$), leisure-time physical activity was included as a predictor of WMH. As WMH was not normally distributed (skewness = 1.61, $SE = 0.35$; kurtosis = 3.51, $SE = 0.68$), a square root transformation was initially performed (Tabachnick & Fidell, 2007) resulting in an improved but still skewed distribution (skewness = 0.79, $SE = 0.35$; kurtosis = 0.82, $SE = 0.68$). A base 10 logarithmic transformation was subsequently performed (Tabachnick & Fidell, 2007), resulting in a normal distribution (skewness = 0.02, $SE = 0.35$; kurtosis = -0.09 , $SE = 0.68$). In the multivariate analyses, common predictors of WMH_{lg10} were added; specifically age, sex and education (see Table 2). Hypertension was not included as a predictor as it was moderately correlated with age, $r = .264$. Other comorbidities were not included as no or few participants reported a history of other comorbidities (see Table 1).

In model 1 of the multivariate analyses (see Table 2), more leisure-time physical activity was associated with less WMH_{lg10} in the active group without a psychiatric history; however, this association was not statistically significant ($b = -.09$, $p > .05$). There was a statistically significant difference in WMH_{lg10} between the more and less active groups without a psychiatric history ($b = .21$, $p = .013$). The entire model explained an adjusted 16% of the variance in WMH_{lg10}, although this was not statistically significant ($p = .06$).

In model 2 of the multivariate analyses (see Table 2), more leisure-time physical activity was associated with more WMH_{lg10} in the active group without a psychiatric history, which was not statistically significant ($b = .15$, $p > .05$). There was not a statistically significant difference in WMH_{lg10} between the more and less active groups without a psychiatric history ($b = .09$, $p > .05$), or between the active group without a psychiatric history and the less active group with a history of depression ($b = .01$, $p > .05$). Model 2 was predictive of WMH_{lg10}, explaining 15% of the variance in WMH_{lg10} ($p = .041$).

Discussion

The current study in cognitively-intact adults examined WMH in those who reported a lifetime of more leisure-time physical activity and had no psychiatric history compared to those who were less active and had no psychiatric history as well as those who were less active and had a history of late-onset depression. Leisure-time physical activity was not significantly associated with WMH in any of the groups when controlling for common predictors of WMH. The results from the current study are consistent with most studies that did not find an association between physical activity and WMH (Carmelli et al., 1999; Ho et al., 2011; Podewils et al., 2007; Rosano et al., 2010; Rovio et al., 2010; Smith et al., 2009; Willey et al., 2011; Zheng et al., 2012). None of the previous literature examined the association between physical activity across the lifespan and WMH. Rovio et al. (2010) and

Carmelli et al. (1999) measured physical activity during midlife 21 and 25 years before measurement of WMH, respectively, and did not find an association between physical activity and WMH. The current study extends the literature by measuring a lifetime of physical activity, as opposed to physical activity at one time point.

The current results contradict literature showing that more physical activity associated with less WMH (Booth et al., 2014; Boots et al., 2014; Gow et al., 2012; Saczynski et al., 2008; Sen et al., 2012; Tseng et al., 2013). However, most previous literature did not control for a psychiatric history (Booth et al., 2014; Boots et al., 2014; Gow et al., 2012; Saczynski et al., 2008; Sen et al., 2012). As depression is associated with more WMH (Herrmann et al., 2008), the current study extends the literature by controlling for any psychiatric history in the more and less active groups. In addition, to our knowledge, this is the first study to examine the association between physical activity and WMH in individuals with a history of late-onset depression but no other psychiatric history.

Some research found physical activity is associated with regional but not total WMH. Tseng et al. (2013) found 10 older adults with more than 15 years of endurance training had less regional but not total WMH than 10 sedentary older adults. Similarly, Suo et al. (2016) found a physical activity intervention reverses regional but not total WMH in cognitively impaired adults. Future studies should measure regional WMH.

Limitations to this study should be noted. Physical activity was based on self-report. However, there are no known objective measures of a lifetime of physical activity. There are two alternative measures of lifetime physical activity; the Historical Leisure Activity Questionnaire (Kriska et al., 1990) and the Modified Historical Leisure Activity Questionnaire which added household physical activities (Chasan-Taber, Erickson, Nasca, Chasan-Taber, & Freedson, 2002). The LTPAQ was chosen because only the LTPAQ assesses all four domains of physical activity (Sallis et al., 2006); occupation, transportation, household, and leisure-time. There was potential recall bias as participants were asked to recall their lifetime physical activity levels. Participants were given a recall calendar to complete before and use during the interview. Although recommendations have been made for measuring physical activity over relatively short reporting intervals, in advanced age long-term memory may be better preserved than recent recollections (Shephard, 2003). Efforts were made to ensure that physical activity was estimated over a period of time long before the typical onset of WMH. Nonetheless, longitudinal designs are necessary to firmly determine the extent to which physical activity affects WMH. Unmeasured genetic and lifestyle factors may have an effect on our findings. We implemented a stringent screening protocol by excluding individuals with any psychiatric history from two groups, including individuals with a history of late-onset depression but no other psychiatric history in a third group, and controlling for potential cardiovascular confounding factors, finding no differences between the groups in terms of a number of factors associated with WMH. To the best of our ability we have minimized the influence of potential confounding factors. Notably, all of the groups were healthier than average community dwellers of similar age. It is possible that the differences in WMH may be found if comparisons are made in population-based samples of adults. This study was based on a small but unique sample size that was entirely White. Thus, the results must be interpreted with caution. The findings of

the present study extend the literature by examining a lifetime of physical activity across multiple domains while accounting for late-onset depression.

Conclusion

We found that in cognitively-intact adults with few co-morbidities, a lifetime of leisure-time physical activity was not associated with WMH. These results held in more and less active individuals without a psychiatric history, as well as less active individuals with a history of late-onset depression but no other psychiatric history.

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Ethical Conduct of Research: Institutional Review Board approval was obtained from the University of Iowa. Individuals were sent an IRB approved letter about the current study, with the principal investigator's contact information. Informed consent was obtained from all participants.

Biographies

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References

- Ainsworth BE, Haskell WL, Whitt MC, Herrmann SD, Meckes N, Bassett DR, ... Leon AS (2011). 2011 Compendium of physical activities: A second update of codes and MET values. *Medicine & Science in Sports & Exercise*, 43, 1575–1581. doi: 10.1249/MSS.0b013e31821ece12
- Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC ... Morris JC (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's Disease. *New England Journal of Medicine*, 367, 795–804. doi: 10.1056/NEJMoa1202753 [PubMed: 22784036]
- Birdsill AC, Kosciak RL, Jonaitis EM, Johnson SC, Okonkwo OC, Hermann BP, ... Bendlin BB (2014). Regional white matter hyperintensities: Aging, Alzheimer's disease risk, and cognitive function. *Neurobiology of Aging*, 35, 769–776. doi: 10.1016/j.neurobiolaging.2013.10.072 [PubMed: 24199558]
- Boisvert-Vigneault K, Payette H, Audet M, Gaudreau P, Bélanger M, & Dionne IJ (2016). Relationships between physical activity across lifetime and health outcomes in older adults: Results from the NuAge cohort. *Preventive Medicine*, 91, 37–42. doi:10.1016/j.ypmed.2016.07.018 [PubMed: 27471024]
- Booth T, Møttus R, Corley J, Gow AJ, Henderson RD, Maniega SM ... Deary IJ (2014). Personality, health, and brain integrity: The Lothian birth cohort study 1936. *Health Psychology*, 33, 1477–86. doi: 10.1037/hea0000012 [PubMed: 24245834]
- Boots EA, Schultz SA, Oh JM, Larson J, Edwards D, Cook D ... Okonkwo OC (2015). Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease. *Brain Imaging and Behavior*, 9, 639–49. doi: 10.1007/s11682-014-9325-9 [PubMed: 25319359]
- Carmelli D, Swan GE, Reed T, Wolf PA, Miller BL, & DeCarli C (1999). Midlife cardiovascular risk factors and brain morphology in identical older male twins. *Neurology*, 52, 1119–1124. doi: 10.1212/WNL.52.6.1119 [PubMed: 10214731]
- Chasan-Taber L, Erickson JB, Nasca PC, Chasan-Taber S, & Freedson PS (2002). Validity and reproducibility of a physical activity questionnaire in women. *Medicine & Science in Sports & Exercise*, 34(6), 987–992. [PubMed: 12048326]
- Crum RM, Anthony JC, Bassett SS, & Folstein MF (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*, 269, 2386–2391. doi: 10.1001/jama.1993.03500180078038 [PubMed: 8479064]
- Cust A, Smith B, Chau J, van der Ploeg H, Friedenreich C, Armstrong B, & Bauman A (2008). Validity and repeatability of the EPIC physical activity questionnaire: A validation study using accelerometers as an objective measure. *The International Journal of Behavioral Nutrition and Physical Activity*, 5, 33. doi: 10.1186/1479-5868-5-33 [PubMed: 18513450]
- Espeland MA, Erickson K, Neiberg RH, Jakicic JM, Wadden TA, Wing RR ... Bryan RN (2016). Brain and white matter hyperintensity volumes after 10 years of random assignment to lifestyle intervention. *Diabetes Care*, 39, 764–771. doi: 10.2337/dc15-2230 [PubMed: 27208378]
- First MB, Spitzer RL, Miriam G, & Williams JB (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute.
- Friedenreich CM, Biel RK, Lau DC, Csizmadia I, Courneya KS, Magliocco AM, ... Cook LS (2011). Case-control study of the metabolic syndrome and metabolic risk factors for endometrial cancer. *Cancer Epidemiology, Biomarkers & Prevention*, 20, 2384–2395. doi: 10.1158/1055-9965.EPI-11-0715
- Friedenreich CM, Cook LS, Magliocco AM, Duggan MA, & Courneya KS (2010). Case-control study of lifetime total physical activity and endometrial cancer risk. *Cancer Causes Control*, 21, 1105–1116. doi:10.1007/s10552-010-9538-1 [PubMed: 20336482]
- Friedenreich CM, Courneya KS, & Bryant HE (1998). The lifetime total physical activity questionnaire: Development and reliability. *Medicine & Science in Sports & Exercise*, 30, 266–274. doi: 10.1097/00005768-199802000-00015 [PubMed: 9502356]

- Friedenreich CM, Courneya KS, Magliocco AM, & Bryant HE (2001). Relation between intensity of physical activity and breast cancer risk reduction. *Medicine and Science in Sports and Exercise*, 33, 1538–1545. doi:10.1097/00005768-200109000-00018 [PubMed: 11528344]
- Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, & Courneya KS (2009). Prospective cohort study of lifetime physical activity and breast cancer survival. *International Journal of Cancer*, 124, 1954–1962. doi:10.1002/ijc.24155 [PubMed: 19123472]
- Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, & Elliott FG (2004). Case-control study of lifetime total physical activity and prostate cancer risk. *American Journal of Epidemiology*, 159, 740–749. doi:10.1093/aje/kwh106 [PubMed: 15051583]
- Gill SJ, Friedenreich CM, Sajobi TT, Longman RS, & Drogos LL, Davenport MH, ... Poulin MJ (2015). Association between lifetime physical activity and cognitive functioning in middle-aged and older community dwelling adults: Results from the Brain inMotion Study. *Journal of International Neuropsychological Society*, 21(10), 816–830. doi:10.1017/S1355617715000880
- Gow AJ, Bastin ME, Maniega SM, Hernandez MCV, Morris Z, Murray C, ... Wardlaw JM (2012). Neuroprotective lifestyles and the aging brain activity, atrophy, and white matter integrity. *Neurology*, 79, 1802–1808. doi: 10.1212/WNL.0b013e3182703fd2 [PubMed: 23091073]
- Herrmann LL, Le Masurier M, & Ebmeier KP (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*, 79, 619–624. doi: 10.1136/jnnp.2007.124651
- Ho A, Raji C, Becker J, Lopez O, Kuller L, Hua X, ... Thompson P (2011). The effects of physical activity, education, and body mass index on the aging brain. *Human Brain Mapping*, 32, 1371–1382. doi: 10.1002/hbm.21113 [PubMed: 20715081]
- Keihaninejad S, Heckemann RA, Fagiolo G, Symms MR, Hajnal JV, Hammers A, & the Alzheimer's Disease Neuroimaging Initiative. (2010). A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). *Neuroimage*, 50, 1427–1437. doi: 10.1016/j.neuroimage.2010.01.064 [PubMed: 20114082]
- Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, ... Kuller LH (1990). Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. *Diabetes Care*, 13(4), 401–411. [PubMed: 2318100]
- Lin JS, O'Connor E, Rossom RC, Perdue LA, & Eckstrom E (2013). Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*, 159, 601–612. doi: 10.7326/0003-4819-159-9-201311050-00730 [PubMed: 24145578]
- Moroni F, Ammirati E, Rocca MA, Filippi M, Magnoni M, & Camici PG (2018). Cardiovascular disease and brain health: Focus on white matter hyperintensities. *International Journal of Cardiology: Heart & Vascular*, 19, 63–69. doi:10.1016/j.ijcha.2018.04.006
- Paradiso S, Naridze R, & Holm-Brown E (2012). Lifetime romantic attachment style and social adaptation in late-onset depression. *International Journal of Geriatric Psychiatry*, 27, 1008–1016. doi: 10.1002/gps.2814 [PubMed: 22147292]
- Podewils LJ, Guallar E, Beauchamp N, Lyketsos CG, Kuller LH, & Scheltens P (2007). Physical activity and white matter lesion progression - Assessment using MRI. *Neurology*, 68, 1223–1226. doi: 10.1212/01.wnl.0000259063.50219.3e [PubMed: 17420407]
- Polit D (2009). *Statistics and Data Analysis for Nursing Research*. New York: Pearson.
- Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L, ... Aizenstein H (2010). Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences*, 65, 639–647. doi: 10.1093/gerona/glq038
- Rovio S, Spulber G, Nieminen LJ, Niskanen E, Winblad B, Tuomilehto J ... Kivipelto M (2010). The effect of midlife physical activity on structural brain changes in the elderly. *Neurobiology of Aging*, 31, 1927–1936. doi: 10.1016/j.neurobiolaging.2008.10.007 [PubMed: 19062136]
- Saczynski JS, Jonsdottir MK, Sigurdsson S, Eiriksdottir G, Jonsson PV, Garcia ME, ... Launer LJ (2008). White matter lesions and cognitive performance: The role of cognitively complex leisure activity. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, 63A, 848–854. doi: 10.1093/gerona/63.8.848

- Sallis JF, Cervero RB, Ascher W, Henderson KA, Kraft MK, & Kerr J (2006). An ecological approach to creating active living communities. *Annual Review of Public Health*, 27, 297–322. doi: 10.1146/annurev.publhealth.27.021405.102100
- Schmidt P, Gaser C, Arsic M, Buck D, Förchler A, Berthele A, ... Mührlau M (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *Neuroimage*, 59, 3774–3783. doi: 10.1016/j.neuroimage.2011.11.032 [PubMed: 22119648]
- Sen A, Gider P, Cavalieri M, Freudenberger P, Farzi A, Schallert M, ... Schmidt H (2012). Association of cardiorespiratory fitness and morphological brain changes in the elderly: Results of the Austrian Stroke Prevention Study. *Neurodegenerative Diseases*, 10, 135–137. doi: 10.1159/000334760 [PubMed: 22269924]
- Shephard RJ (2003). Limits to the measurement of habitual physical activity by questionnaires. *British Journal of Sports Medicine*, 37, 197–206, discussion 206. doi: 10.1136/bjsm.37.3.197 [PubMed: 12782543]
- Smith JA, Turner ST, Sun YV, Fornage M, Kelly RJ, Mosley TH, ... Kardia SL (2009). Complexity in the genetic architecture of leukoaraiosis in hypertensive sibships from the GENOA Study. *BMC Medical Genomics*, 2, 16. doi: 10.1186/1755-8794-2-16 [PubMed: 19351393]
- Suo C, Singh MF, Gates N, Wen W, Sachdev P, Brodaty H, ... Valenzuela MJ (2016). Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. *Molecular Psychiatry*, 21, 1633–1642. doi:10.1038/mp.2016.19 [PubMed: 27001615]
- Tabachnick BG, & Fidell LS (2007). *Using multivariate statistics* (5th ed.). New York: Pearson Education.
- Tam C, Li Q, Friedenreich C, Martin LJ, Hislop G, Hanley AJ, ... Boyd NF (2014). Lifetime physical activity in postmenopausal Caucasian and Chinese-Canadian women. *European Journal of Cancer Prevention*, 23, 90–95. doi:10.1097/CEJ.0b013e32836162c6 [PubMed: 23571512]
- Topolski T, LoGerfo J, Patrick D, Williams B, Walwick J, & Patrick M (2006). The Rapid Assessment of Physical Activity (RAPA) among older adults. *Preventing Chronic Disease*, 3, A118–A118. doi: 10.12968/ijtr.2014.21.10.469 [PubMed: 16978493]
- Torres ER (2018). Validation of the Lifetime Total Physical Activity Questionnaire (LTPAQ) in adults with a history of late-onset depression. *Archives of Psychiatric Nursing*, 32, 580–584. doi: 10.1016/j.apnu.2018.03.015 [PubMed: 30029751]
- Torres ER, Strack EF, Fernandez CE, Tumey TA, & Hitchcock ME (2015). Physical activity and white matter hyperintensities: A systematic review of quantitative studies. *Preventive Medicine Reports*, 2, 319–325. doi:10.1016/j.pmedr.2015.04.013 [PubMed: 26046015]
- Tseng BY, Gundapuneedi T, Khan MA, Diaz-Arrastia R, Levine BD, Lu H, ... Zhang R (2013). White matter integrity in physically fit older adults. *Neuroimage*, 82, 510–516. doi: 10.1016/j.neuroimage.2013.06.011 [PubMed: 23769914]
- Wiley JZ, Moon YP, Paik MC, Yoshita M, DeCarli C, Sacco RL, ... Wright CB (2011). Lower prevalence of silent brain infarcts in the physically active The Northern Manhattan Study. *Neurology*, 76, 2112–2118. doi: 10.1212/WNL.0b013e3281f4472 [PubMed: 21653889]
- Zheng JJ, Delbaere K, Close JCT, Sachdev P, Wen W, Brodaty H, & Lord SR (2012). White matter hyperintensities are an independent predictor of physical decline in community-dwelling older people. *Gerontology*, 58, 398–406. doi: 10.1159/000337815 [PubMed: 22614074]

Table 1

Description of Sample

	PA Group (n = 20)	No Depression Group (n = 13)	Depression Group (n = 14)	p-value
Mean (SD)				
Age (years)	62.1 (7.1)	64.0 (6.7)	62.8 (7.1)	.75
Leisure-time PA	26.9 (22.1)	15.2 (9.3)	12.4 (9.4)	.036
Occupation PA	56.7 (30.5)	58.8 (48.8)	84.1 (81.7)	.69
Transportation PA	2.4 (1.8)	2.0 (2.4)	1.6 (1.5)	.41
Household PA	50.1 (65.5)	59.6 (59.0)	87.7 (72.7)	.18
Total PA	135.9 (67.4)	135.3 (74.7)	185.8 (93.6)	.15
Mini-Mental Status Exam	29.2 (1.3)	29.8 (0.4)	29.5 (0.8)	.40
White Matter Hyperintensities	2.0 (1.1)	3.0 (1.3)	2.8 (1.9)	.021
N (%)				
Female	13 (44.9)	7 (24.1)	9 (31.0)	.79
Education				.22
Up to High School Some College	2 (4.3)	1 (2.1)	2 (4.3)	
Some College	1 (2.1)	3 (6.4)	2 (4.3)	
Associate's Degree	1 (2.1)	3 (6.4)	1 (2.1)	
Bachelor's Degree	9 (19.1)	1 (2.1)	8 (17.0)	
Master's Degree	4 (8.5)	3 (6.4)	1 (2.1)	
Professional degree, i.e. PhD, MD, JD	3 (6.4)	2 (4.3)	0	
History of Hypertension	4 (33.3)	5 (41.7)	3 (25.0)	.45
History of Coronary Heart Disease	0	0	1	.30
History of Left Ventricular Hypertrophy	0	0	0	--
History of Congestive Heart Failure	0	0	0	--
History of Atrial Fibrillation	0	0	0	--
History of Diabetes	0	1 (50.0)	1 (50.0)	.46
History of Dyslipidemia	1 (5.0)	2 (28.6)	0	.25

Note. ^aPA = Physical Activity measured in MET- hours per week per year

Table 2.**Multiple Regression of Predictors of White Matter Hyperintensities**

Model	Predictor	<i>b</i>	<i>SE</i>	β	<i>t</i>	<i>p</i>	R^2	R^2 Adjusted	Overall Significance
1							.27	.16	.06
	More Active, No Depression Group	-.09	.43		-.21	.83			
	Less Active, No Depression Group	.21	.08	.44	2.64	.013			
	Age	.01	.01	.13	.73	.47			
	Sex	-.05	.09	-.11	-.60	.55			
	Education	.02	.03	.12	.74	.47			
2							.24	.15	.041
	More Active, No Depression Group	.15	.32		.49	.63			
	Less Active, No Depression Group	.09	.05	.31	1.83	.07			
	Less Active, Depression Group	.01	.05	.05	.31	.76			
	Age	.00	.00	.14	1.00	.32			
	Sex	-.12	.07	-.24	-1.73	.09			
	Education	-.01	.02	-.06	-.41	.69			