Published in final edited form as:

Behav Brain Res. 2016 January 1; 296: 118–124. doi:10.1016/j.bbr.2015.09.005.

Association of change in brain structure to objectively measured physical activity and sedentary behavior in older adults: Age, Gene/Environment Susceptibility-Reykjavik Study

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Abstract

Many studies have examined the hypothesis that greater participation in physical activity (PA) is associated with less brain atrophy. Here we examine, in a sub-sample ($n = 352$, mean age 79.1 years) of the Age, Gene/Environment Susceptibility-Reykjavik Study cohort, the association of the baseline and 5-year change in magnetic resonance imaging (MRI)-derived volumes of gray matter (GM) and white matter (WM) to active and sedentary behavior (SB) measured at the end of the 5-year period by a hip-worn accelerometer for seven consecutive days. More GM ($\beta = 0.11$; $p = 0.044$) and WM ($\beta = 0.11$; $p = 0.030$) at baseline was associated with more total physical activity (TPA). Also, when adjusting for baseline values, the 5-year change in GM ($\beta = 0.14$; $p = 0.0037$) and WM ($\beta = 0.11$; $p = 0.030$) was associated with TPA. The 5-year change in WM was associated with SB ($\beta = -0.11$; $p = 0.0007$). These data suggest that objectively measured PA and SB late in life are associated with current and prior cross-sectional measures of brain atrophy, and that change over time is associated with PA and SB in expected directions.

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Disclosure statement

The authors have no conflicts to disclose.

Keywords

Physical activity; Sedentary behavior; Brain atrophy; Elderly; MRI

1. Introduction

It is hypothesized that physical activity (PA) helps to preserve and maintain cognitive function and decrease the risk of dementia and Alzheimer disease [1–4]. Change in cognitive ability has been associated with brain atrophy [5–17]. It has been shown that the brain atrophies with age due to volume loss in both white (WM) and gray matter (GM) and increase in white matter lesions [18]. GM has been shown to linearly decline with increasing age starting at early adulthood, while WM deterioration shows nonlinear changes [14,19,20]. WM has been shown to increase throughout adulthood, peaking at around the age of 40–60 years, followed by an accelerated decline starting around age 60 [14,19]. PA is also known to be negatively associated with age [21,22] and sedentary behavior (SB) is known to be positively associated with age [23]. This trend has been shown to start in the forties [22].

Cross-sectional studies have shown a positive relationship between GM and WM volumes in the older adult brain and physical fitness [24,25]. Furthermore, six months aerobic training was shown to increase both GM and WM volumes in older subjects [26]. A cross-sectional study, using questionnaire, showed PA levels to positively correlate with brain volumes [27]. Longitudinal studies, using questionnaires have shown that higher level of PA at baseline predicts larger GM volume [28–30], larger WM volume [29] and more total brain volume [29,30] in late life. Studies using objectively measured PA are needed to confirm these results.

Previous studies have shown that lower PA levels predict lower brain volumes and atrophy [28–30], indicating that PA affects brain volumes. Currently, there are no published studies on whether brain volumes or changes in brain volume, is associated with PA later in life. It might be expected that those with greater PA would have a history of greater brain volumes both in the past and in the present and show the best maintenance of brain volumes over time. The aims of this study are to quantify the prospective changes in magnetic resonance imaging (MRI)-derived brain atrophy measurements in a 5-year period and explore their association with objectively measured PA and SB in an older population. This study is the first to assess brain atrophy in a longitudinal study design in relation to objectively measured behavior outcomes. Furthermore, we will test the hypothesis that the association between brain volumes and the important behavioral variables, PA and SB, are independent of self-reported PA at baseline (SPA).

2. Methods

2.1. Study population and design

The Age, Gene/Environment Susceptibility Reykjavik Study (AGES-Reykjavik study) was a prospective cohort study designed to examine risk factors in relation to disease and disability in old age. The aim was to investigate the contributions of environmental factors, genetic

susceptibility, and gene-environment interactions to aging of the neurocognitive, cardiovascular, musculoskeletal, body composition, and metabolic systems. The AGES-Reykjavik study is a continuation of the Reykjavik Study, which was initiated in 1967 by the Icelandic Heart Association and included men and women born in 1907–1935 and living in the Reykjavik area. From 2002 to 2006, new data were collected for the AGES-Reykjavik study, and details on the study design have been described elsewhere [31]. Data from this data collection was used as baseline measurements for the current study. The current study was a part of the AGESII-Reykjavik study which is a follow up of the AGES-Reykjavik study, with the time interval of approximately five years. Between April 2009 and June 2010, objective PA measurement by accelerometers was added to the AGESII-Reykjavik study test protocol [21]. During the PA sub-study measurement period, 1194 subjects participated in the AGESII-Reykjavik study and were eligible to be invited to participate in the sub-study. Of these, 150 participants were excluded for different reasons (e.g., blindness and other physical- and mental impairments), 84 refused and 294 did not participate because of scheduling conflicts. Five subjects lost the accelerometers. The remaining 671 (56.2%) participants received an accelerometer to measure their daily activity. Of these, 585 participants had four or more valid days (10 h of wear time) of useable accelerometry data. After excluding those with mild cognitive impairment (MCI), dementia or scored 24 or less on MMSE, 18 or less on the DSST test and did not have both brain measurements in AGES-Reykjavik study and AGESII-Reykjavik study, the final number of subjects was 352. The study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority, and the institutional review board of the US National Institute on Aging, National Institutes of Health. Signed informed consent was given by all participants.

2.2. Assessment of PA

Participants were asked to wear the ActiGraph GT3X accelerometer (Actigraph Inc., Pensacola FL) monitor at the right hip for one complete week and to remove the monitor only before going to bed and during showers, bathing, or other water activities. Non-wear was defined as a period of at least 60 consecutive minutes during which the activity monitor recorded zero counts in all axes, allowing 1–2 min of vertical-axis counts between 0 and 100. A day of accelerometer wear was considered valid if the wear time was 10 h. Participants with fewer than four valid days over the week of measurement were excluded. Activity variables were derived from vertical-axis count values, and included: Total PA (TPA) defined as total counts during an average day ($\text{counts} \times \text{day}^{-1}$) and SB as hours $\times \text{day}^{-1}$ of activity $< 100 \text{ count} \times \text{min}^{-1}$ during wear time. Lifestyle PA was defined as $760 \text{ counts} \times \text{min}^{-1}$ [21,32,33].

2.3. MRI image acquisition

MRI including T1-, proton density-, and T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were acquired on a 1.5-Tesla Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI) in the AGES-Reykjavik study. Brain tissue volumes, including GM, WM, cerebral spinal fluid (CSF), and white matter hyperintensities (WMH), were generated separately, using the multispectral MR images and a high-throughput automatic image analysis pipeline, which is based on the Montreal

Neurological Institute (MNI) pipeline and optimized for use in the AGES-Reykjavik study (AGES-RS/MNI pipeline) [18]. The key processing stages were as follows: stereotaxic registration was achieved after signal non-uniformity correction by an affine transformation of the T1-weighted images to the ICBM152 template. Intersequence registration was performed by registering images from the individual (T2/proton density, fluid-attenuated inversion recovery) sequences to the T1-weighted images in order to accurately align all image volumes acquired during an acquisition session. Linear signal intensity normalization was then applied to correct for signal intensity variations across images in the different sequences. Finally, tissue classification was achieved with an artificial neural network classifier. The absolute volumes of the four tissue types were subsequently calculated and converted to native space volumes using the scale factor obtained from the stereotaxic registration transformation. Intra-cranial volume (ICV) was calculated by adding the volumes of GM, normal WM, WMH and CSF. All tissue volumes are presented as percent of the total ICV. The acquisition and post-processing of the MRI have been described in detail elsewhere [18]. The methods used in the follow-up MRI were the same as used in the baseline measurements. The 5-year change () in GM and WM volumes was calculated as the difference between the relative volume at follow-up and baseline.

2.4. Covariates

Covariates measured at baseline included age, sex and education [34]. Weight and body mass index (BMI) [35] was measured at follow-up. BMI was calculated as weight [kg] divided by squared height [m²]. Education was categorized as primary, secondary, college and university degree. SPA gathered from questionnaires from the AGES-Reykjavik study at baseline. Participants answered questions about how often they had participated in moderate or vigorous PA in the past 12 months (six categories to answer; (1) never, (2) rarely, (3) weekly but less than 1 h/week, (4) 1–3 h/week, (5) 4–7 h/week or (6) more than 7 h/week). The questions regarding PA were answered on a take-home questionnaire, that was reviewed by a trained interviewer when the participant came to a second visit to the clinic and returned the questionnaire. The following health factors measured at baseline were also used for adjustments: number of brain infarcts [18] depression [36], type 2 diabetes [37,38], mean arterial pressure (MAP) [39] and smoking status [30,38]. The presence of depression was assessed using the MINI International Neuropsychiatric Interview [40]. Participants were eligible for the MINI Interview if they had a score ≥ 6 on the 15-item Geriatric Depression Scale [41], had a history of anxiety or depression or were taking anti-depressant medication. Type 2 diabetes was defined as a fasting blood glucose level ≥ 7.0 mmol/L, the use of diabetic medication, or self-report of physician's diagnosis of diabetes. MAP was calculated from the participants diastolic- (DP) and systolic (SP) pressure ($MAP = DP + [1/3] \times [SP - DP]$). Smoking status was assessed by questionnaire and assigned as current/former smoker versus never smoked. SB was adjusted for lifestyle PA and wear time in all statistical models.

Analyses were performed using IBM SPSS 20.0 (SPSS Inc., Chicago, IL). The association between the accelerometer variables and brain volume measurements was analyzed using linear regression models. The PA variables were log transformed to correct for skewness. For Tables 2 and 3, linear regressions were performed and several models were formed.

First, Model 1 was adjusted for age and sex and coefficients reflect association for individual brain volume measurements variables in separate models. In Model 2 each brain volume variable was adjusted for age, sex, brain infarcts, days between baseline and follow-up measurements, SPA, BMI, depression, MAP, type 2 diabetes, smoking status and education. Further, in Model 3, all baseline measurement variables and 5-year change variables were entered in the same model adjusted for same covariates as in Model 2.

3. Results

3.1. Descriptive statistics

Descriptive characteristics for women and men are presented in Table 1. Participants were also subdivided into those with high (above median) and low (below median) baseline volumes of both GM and WM. TPA and SB for men and women, for low and high GM, and for low and high WM, are presented in Fig. 1 and Fig. 2, respectively. The mean age of the participants receiving an accelerometer at the AGESII-Reykjavik study was 79.1 (SD 4.4) years. Participants with lower GM averaged 106,000 counts $\times$ day⁻¹ in TPA, but those with higher GM averaged 127,000 counts $\times$ day⁻¹ in TPA. Participants with lower WM averaged 101,000 counts $\times$ day⁻¹ in TPA, but those with higher WM averaged 132,000 in counts $\times$ day⁻¹ in TPA. For SB, those with lower GM spent 10:20 h:min $\times$ day⁻¹ sedentary, but those with higher GM spent 10:11 h:min $\times$ day⁻¹ sedentary. Participants with lower WM spent 10:30 h:min $\times$ day⁻¹, but those with higher WM spent 10:01 h:min $\times$ day⁻¹ in SB.

3.1.1. Regression analysis of physical activity and brain volume—Results from linear regression models for TPA are shown in Table 2. With adjustments for age and sex (Models 1), all brain measurement variables were separately and significantly positively associated with TPA (all $p < 0.05$), except the 5-year change in WM. Adding brain infarcts, days between baseline and follow-up measurements, SPA, BMI, depression, MAP, type 2 diabetes, smoking status and education as covariates (Model 2), did not change the significance or direction of the correlations, with the exception of the 5-year change in WM, which was found to have a significant, positive correlation with TPA ($p < 0.05$). When both baseline brain volume and the 5-year brain volume change were included in the same model (Model 3), which also adjusted for the above potential confounding variables, all brain volumes were significantly associated with TPA (all $p < 0.05$). Less brain volume at baseline and more 5-year loss, predict less PA.

3.1.2. Regression analysis of sedentary behavior and brain volume—Results from linear regression models for SB are shown in Table 3. For SB, only WM at follow-up ($\beta = -0.092$; $p = 0.0032$) and the 5-year change in WM ($\beta = -0.080$; $p = 0.0051$) were separately associated, negatively, with SB. Less WM at baseline and more 5-year decrease, predict more SB. When adjusting the models for the above covariates, lifestyle PA and wear time, the same brain parameters were significantly negatively associated with SB (WM at follow-up: $\beta = -0.084$; $p = 0.012$); (5-year change in WM: $\beta = -0.10$; $p = 0.0010$). These associations remained in Model 3.

4. Discussion

The main finding of this study is that more GM and WM at both baseline and follow-up are independently associated with more TPA, even when adjusted for self-reported PA questionnaire (SPA) and several other potential confounding variables. Furthermore, a 5-year change in both GM and WM was associated with less TPA. In addition, less WM at follow-up and the 5-year change in WM was independently associated with more SB, also after adjusting for lifestyle PA, wear time, SPA and other potential confounding variables. The results suggest that maintenance of brain volume is associated with PA in older adults and that WM atrophy is associated with SB, independent of lifestyle PA and SPA. Thus: (a) more GM and WM volumes, and less 5-year atrophy in these volumes, predicts more PA; and (b) more 5-year atrophy in WM, predicts more SB.

Previous longitudinal studies have shown higher PA and structured exercise to be associated with more global or regional brain volumes later in life, both GM and WM [28–30,42]. Most of those studies use self-reported questionnaires which are known to misestimate PA levels and SB in comparison to more objective measurements [43,44]. Interestingly, two longitudinal studies found no association between PA and brain volumes after adjusting for confounding factors [29,30]. However, in both studies the participants were slightly younger than in the present study. In the present study, we adjust for PA measured at baseline with questionnaire (SPA) when examining change in the brain measurements. Therefore, the observed association between brain volumes and brain volume changes on the one hand, and PA and SB at follow-up on the other hand, are independent of the SPA classification at baseline. Our results thus may suggest that the longitudinal relationship between brain volumes and PA could also be the other way around, i.e. brain atrophy associates with subsequent decline in PA and more SB. This bidirectional relationship, i.e. brain atrophy causes less PA and vice versa, forms a pattern that needs intervention. By breaking that bidirectional relationship, better physical- and brain health could be gained.

Only the 5-year decrease in WM independently predicted more SB after adjusting for lifestyle PA, wear time and potential confounding variables. In older people, SB is known to have the highest prevalence of all activity types compared to any other age group [23,45,46]. We have previously shown in this cohort that participants were on average sedentary for 10.1 h × day, or 74.5% of their non-sleeping time [21]. The increase in time spent in SB after the age of 60 may be due to positive factors such as increased leisure time following retirement or to negative factors such as worsening health conditions [23]. SB has been identified as a distinct risk factor for poor health [47] and mortality [48]. With increasing age, nerve fiber activity declines and affects brain function [49,50]. A recent study suggests that among older adults, the structural integrity of WM is not only dependent on levels of PA, but also on the amount of remaining time spent sedentary [51].

Future studies should also investigate whether atrophy of particular regions in the brain are more potent than other regions in terms of diminishing PA and increasing SB. Many studies have demonstrated the effects of both planned exercise and PA in changing the volume of most regions of the brain [26–28,30,35,42,52–55]. Blood flow in the brain has been shown to vary between types of exercise and intensities [56,57]. Furthermore, it has been well

documented that increased blood flow in the brain during exercises promotes the development of new neurons [58–60] and thereby delays brain structural and functional decline [61]. Although, PA seems to affect some regions of the brain more than others, it cannot be assumed that the atrophy of the same regions are most potent in affecting the PA and SB.

The present study is based on the well-characterized, population based AGES-Reykjavik cohort of older men and women [31]. This cohort consists of healthy older adults of Caucasian descent. It is thus expected that these findings can be generalized for most western populations in this age range. The main strengths of this study include objectively measured PA at study follow-up. Also, we have a longitudinal design of brain measurements with five years interval. Earlier it has been shown that participants who wore the accelerometers had similar characteristics compared with those participants who did not receive an accelerometer [21]. Nonetheless, we acknowledge several limitations in the present study. PA at baseline was not measured by an objective method, as self-report questionnaires were used. Therefore, we did not have similar measurements of the PA and SB at baseline and at follow-up, and SB was not measured at baseline. It is possible that if objective measurement of PA at baseline would have been available and used to adjust the statistical models, the observed association would have become attenuated. A longitudinal study using objective measurements both at baseline and follow-up would be beneficial to further test our hypothesis. Also, even though objective measurements are considered to be more accurate than subjective measurements, it is known that hip-worn accelerometers fail to detect some movements, like upper body movements during activities such as weight lifting and heavy carrying. They also have limitations on detecting non-ambulatory activities like cycling [62], activity that is not common in this age group in Iceland [63]. However, a quarter of the participants in this cohort of older Icelanders, reported swimming as an exercise [21], which is not included in the presented TPA. Since we only have objective measurements at follow-up, it is unclear if the relationships observed are uni- or bi-directional. Other studies are necessary to identify the direction of these relationships.

5. Conclusions

Our study confirms that there is an association between brain atrophy and PA. We also show an association between brain atrophy and SB, independent of lifestyle PA. These relationships are robust to adjustment by a number of confounders. This study provides additional evidence of the positive association of PA and the brain. PA interventions aimed at alleviating this association could have important public health impact.

Acknowledgments

This study has been funded by NIA contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). This work was also supported by the National Science Foundation Graduate Research Fellowship under Grant No. DGE-0940903 and by the National Institutes of Health Intramural Research Program, grant number: Z01 DK071013 and Z01 DK071014 to RJB and KYC. Thor Aspelund is acknowledged for statistical consultation. The researchers are indebted to the participants for their willingness to participate in the study.

Abbreviation

AGES-Reykjavik study

Age, Gene/Environment Susceptibility Reykjavik Study

AGESII-Reykjavik study

Age, Gene/Environment Susceptibility Reykjavik Study, second phase

BMI

body mass index

CSF

cerebral spinal fluid

DP

diastolic pressure

GM

gray matter

ICV

intra-cranial volume

MAP

mean arterial pressure

MRI

magnetic resonance imaging

SB

sedentary behavior

SP

systolic pressure

SPA

self-reported PA questionnaire

PA

physical activity

WM

white matter

WMH

white matter hyperintensities

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HIGHLIGHTS

- Accelerometer was used to measure physical activity and sedentary behavior at follow up.
- Gray matter and white matter was measured both at baseline and follow up, with 5-year interval.
- An association was found between brain atrophy and physical activity.
- There was also an association between brain atrophy and sedentary behavior, independent of lifestyle physical activity.

Fig. 1.
The mean ($\pm$ SD) amount of total physical activity (TPA) for men and women, those with low gray matter (GM) and high GM, and those with low white matter (WM) and high WM.

Fig. 2.
The mean ($\pm$ SD) amount of sedentary behavior (SB) for men and women, those with low gray matter (GM) and high GM, and those with low white matter (WM) and high WM.

Table 1

Descriptive statistics for participants ($n=352$) shown separately for women and men, for those above (GM high) and below the median for GM at baseline (GM low), and for those above (WM high) and below (low WM) the median for WM at baseline. Data are presented as mean ($\pm$ SD).

Demographics	Men ($n=137$)	Women ($n=215$)	GM low($n=176$) ^a	GM high($n=176$) ^a	WM low($n=176$) ^a	WM high ($n=176$) ^a
Age ^a	79.2 (4.0)	79.0 (4.6)	80.3 (4.6)	77.9 (3.7)	80.6 (4.5)	77.6 (3.7)
BMI ($\text{kg} \times \text{m}^{-2}$) ^a	26.9 (3.8)	26.9 (4.7)	26.2(4.2)	27.6 (4.4)	27.1 (4.4)	26.8 (4.3)
Weight (kg) ^a	83.9 (13.6)	70.9 (13.4)	75.4(15.1)	76.5 (14.7)	76.2 (15.9)	75.6 (13.9)
ICV(cm^3) ^b	1617 (122)	1409 (96)	1544 (145)	1435 (129)	1489 (144)	1490 (151)
GM (%) ^{b, c}	45.1 (2.7)	47.3 (2.7)	44.3 (1.9)	48.7 (1.7)	46.0 (2.8)	47.0 (2.9)
WM (%) ^{b, c}	26.1 (1.6)	26.2 (1.7)	26.0(1.7)	26.4 (1.6)	24.9 (1.1)	27.5 (0.89)
GM-5yr(%) ^{a, c}	43.9 (2.7)	46.7 (2.8)	43.4(2.1)	47.9 (1.9)	45.0 (3.0)	46.2 (3.0)
WM-5yr(%) ^{a, c}	24.7 (1.9)	24.9 (1.9)	24.5 (1.9)	25.1 (1.8)	23.4 (1.4)	26.2 (1.1)
-GM (%) ^d	-1.2 (1.1)	-0.65 (1.0)	-0.91 (1.2)	-0.85 (0.93)	-0.92(1.2)	-0.83 (1.0)
-WM (%) ^d	-1.3 (0.83)	-1.4 (0.67)	-1.5 (0.82)	-1.2 (0.62)	-1.4 (0.81)	-1.3 (0.65)
Wear time (h:min $\times$ day ⁻¹) ^a	13:59 (1:18)	13:47 (1:13)	13:45 (1:20)	13:58 (1:10)	13:46 (1:20)	13:57 (1:10)
SB (h:min $\times$ day ⁻¹) ^a	10:31 (1:27)	10:06 (1:23)	10:20 (1:21)	10:11 (1:29)	10:30 (1:27)	10:01 (1:21)
TPA(1000 counts $\times$ day ⁻¹) ^a	120 (68)	114 (61)	106 (56)	127 (69)	101 (57)	132 (67)
Wear time PA (counts $\times$ min ⁻¹) ^a	143 (81)	136 (70)	127 (65)	151 (81)	121 (67)	157 (77)

BMI = Body mass index; ICV = intra-cranial volume; GM = gray matter, WM = white matter, PA = physical activity; SB = sedentary behavior.

^a Follow-up (5-yr) measurements.

^b Baseline measurements.

^c Brain volumes as percent of ICV.

^d 5-year change (follow-up – baseline) ().

Table 2

Association between brain atrophy measures and total objectively measured physical activity. Brain volume measurements are presented as a percent of intra-cranial volume.

Variables	Total physical activity (counts $\times$ day ⁻¹)				
	Std. β	Lower 95% CL	Upper 95% CL	P	
Model 1 [#]					
GM ^a	0.16	0.047	0.27	0.0056	
WM ^a	0.20	0.093	0.31	0.00030	
GM-5yr ^b	0.24	0.12	0.35	<0.0001	
WM-5yr ^b	0.22	0.11	0.33	<0.0001	
-GM ^c	0.17	0.063	0.27	0.0016	
-WM ^c	0.090	-0.011	0.19	0.080	
Model 2 ^{##}					
GM ^a	0.12	0.012	0.23	0.029	
WM ^a	0.13	0.031	0.23	0.010	
GM-5yr ^b	0.17	0.063	0.28	0.0021	
WM-5yr ^b	0.16	0.062	0.26	0.0016	
-GM ^c	0.11	0.015	0.21	0.024	
-WM ^c	0.11	0.0095	0.20	0.032	
Model 3 ^{###}					
GM ^a	0.11	0.0028	0.22	0.044	
WM ^a	0.11	0.011	0.21	0.030	
-GM ^c	0.14	0.047	0.24	0.0037	
-WM ^c	0.11	0.010	0.21	0.030	

GM =gray matter, WM =white matter.

[#]Model 1 =each variable entered separately and adjusted for age and sex.

^{##}Model 2 = Model 1 and additional adjustment for brain infarcts, days between baseline and follow-up measurements, education, SPA, BMI, depression, MAP, type 2 diabetes, smoking status and education.

^{###}Model 3 = baseline and the 5-year change brain measurement variables () included in the same model with same adjustments as in model 2.

^aBaseline measurement.

$$\dot{S}_q(t) = \text{change in } S_q \text{ over time } t$$

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Table 3

Association between brain atrophy measures and objective sedentary behavior. Brain volume measurements are presented as a percent of intracranial volume.

Variables	Sedentary behavior (hours × day ⁻¹)			
	Std. β	Lower 95% CL	Upper 95% CL	p
Model 1 #				
GM ^a	-0.011	-0.075	0.054	0.74
WM ^a	-0.061	-0.12	0.00082	0.053
GM-5yr ^b	-0.023	-0.091	0.044	0.49
WM-5yr ^b	-0.092	-0.15	-0.031	0.0032
-GM ^c	-0.026	-0.085	0.033	0.38
-WM ^c	-0.080	-0.14	-0.024	0.0051
Model 2 ##				
GM ^a	-0.0042	-0.074	0.065	0.91
WM ^a	-0.043	-0.11	0.022	0.19
GM-5yr ^b	-0.011	-0.083	0.061	0.76
WM-5yr ^b	-0.084	-0.15	-0.019	0.012
-GM ^c	-0.015	-0.077	0.047	0.64
-WM ^c	-0.10	-0.17	-0.042	0.0010
Model 3 ###				
GM ^a	0.015	-0.056	0.085	0.68
WM ^a	-0.037	-0.10	0.028	0.26
-GM ^c	-0.034	-0.10	0.029	0.28
-WM ^c	-0.11	-0.17	-0.047	0.0007

GM = gray matter, WM=white matter.

Model 1 = each variable entered separately and adjusted for age and sex, wear time and lifestyle PA.

Model 2 = Model 1 and additional adjustment for brain infarcts, days between baseline and follow-up measurements, education, SPA, BMI, depression, MAP, type 2 diabetes, smoking status and education.

Model 3 = baseline and the 5-year change brain measurement variables () included in the same model with same adjustments as in model 2.

^a Baseline measurement.

.() (online) follow-up change δ_2
 treatment measurement follow-up δ_2

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