Relation between physical activity and cerebral small vessel disease. A 9-year prospective cohort study.

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Abstract

Background and aims: Given the unexplored potential of physical activity to reduce the progression of cerebral small vessel disease (cSVD), the purpose of this study was to prospectively (across 9-year follow-up) examine the relation between (baseline) physical activity and the (clinical and imaging) consequences of the whole spectrum of cSVD.

Methods: 503 Patients with cSVD from the RUNDMC study were followed for 9 years. Physical activity was assessed using a questionnaire in 2006, 2011 and 2015. Clinical events (i.e. all-cause mortality, cerebrovascular events (by stroke subtype) were collected with a structured questionnaire. Patients underwent MRI scanning for the assessment of MRI-markers of cSVD (i.e. white matter hyperintensities, lacunes and microbleeds) and microstructural integrity of the white matter at three timepoints.

Results: The mean age at baseline was 66 (SD 9.0) years; 44% were women. A higher baseline physical activity level was independently associated with a lower all-cause mortality (HR: 0.69, 95%CI: 0.49-0.98, p=0.03) and incidence of cerebrovascular disease (HR: 0.58, 95%CI: 0.36-0.96, p=0.03). However, we found no relation between physical activity and incident lacunar stroke or progression of MRI markers of cSVD.

Conclusions: Whilst regular physical activity was not related to the progression of MRI markers of cSVD across a 9-year follow-up, results from our study prove that high levels of physical activity in patients with cSVD are associated with a lower all-cause mortality and lower incidence of cerebrovascular events.

Introduction

Cerebral small vessel disease (cSVD) refers to a group of several pathological processes affecting the small arteries, arterioles, capillaries and venules of the brain.[1-3] Patients with cSVD are at an increased risk of clinical symptomatic cerebrovascular disease (i.e. stroke and transient ischemic attack (TIA)) and vascular dementia, ultimately causing (long-term) disability and mortality[4, 5]. Given the small size of these affected vessels, they cannot be visualized in-vivo individually. However, the presumed consequences of cSVD can be visualized on conventional MRI and diffusion tensor imaging (DTI) ranging from generalized brain atrophy, white matter hyperintensities (WMH) and lacunes of presumed vascular origin to lower microstructural integrity [6, 7].

Unfortunately, there is no proven effective treatment to attenuate the progression of cSVD, which emphasizes the need for the identification of new treatable targets. Given its ability to improve vascular risk factors that are related to cSVD[8, 9], physical activity (PA) may potentially be an effective strategy in preventing clinical events and/or progression of cSVD. In support of this hypothesis, one study has found better microstructural integrity (i.e. higher fractional anisotropy (FA) and lower mean diffusivity (MD)) and fewer white matter hyperintensities (WMH) in physically active cSVD patients compared to their sedentary peers[10]. An important limitation of this latter study was the cross-sectional nature, which complicates the determination of direction of causality. Moreover, the effects of PA likely take a long period (i.e. months to years),[8, 9] highlighting the need to examine the impact of PA on clinical events and progression of cSVD disease using a longitudinal design.

Aims and hypothesis

Therefore, the aim of this study was to examine both the cross-sectional and prospective (across 9-year follow-up) relation between baseline PA and the development of clinical events and MRI markers of cSVD to assess progression of the disease. We hypothesized, following the results from cross-sectional observations, that higher levels of PA are also longitudinally related to fewer clinical events, slower progression of MRI markers of cSVD and better preservation of white matter (micro)structure.

Methods

Study population

Patients with cSVD were included for the Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUNDMC) study, a prospective study that investigates risk factors and clinical consequences of cSVD. Inclusion of these individuals was performed in 2006, with follow-up measurements in 2011 and 2015. All participants signed an informed consent form. The study has been approved by the relevant ethical committee (CMO Arnhem-Nijmegen).

In 2006, patients with symptomatic cSVD referred to the Department of Neurology of the Radboud university medical centre (Radboudumc) between October 2002 and November 2006 were selected for participation. Inclusion criteria were 1) age between 50 and 85 years, and 2) established cSVD, either based on neuroimaging (WMH and/or lacunar infarcts) or on a lacunar syndrome >6 months after the event. Exclusion criteria were 1) dementia (American Psychiatric Association, 2000); 2) Parkinson(ism); 3) intracranial haemorrhage; 4) life expectancy of < 6 months; 5) intracranial space occupying lesions; 6) (psychiatric) disease interfering with cognitive testing or follow-up; 7) recent or current use of acetylcholine-esterase inhibitors, neuroleptic agents, L-dopa or dopa-agonists/antagonists; 8) non-SVD related white matter

lesion mimics (e.g. multiple sclerosis); 9) prominent visual or hearing impairment; 10) language barrier; and 11) MRI contra-indications or known claustrophobia. From 1,004 invited patients, 727 were eligible for participation. Ultimately, 525 individuals agreed to participate and signed informed consent. A total of 22 individuals were excluded during these tests, as exclusion criteria were found during this visit. Complete information, including a cerebral MRI scan, was obtained for 503 individuals. These participants reported (a combination of) symptoms consisting of TIA or lacunar syndrome (n=219), cognitive disturbances (n=245), motor disturbances (n=97) and/or depressive symptoms (n=100). Baseline characteristics and vascular risk factors for all patients were extracted from the RUNDMC database.

Assessment of physical activity

Physical activity was prospectively assessed in 2006, 2011 and 2015 with a questionnaire that has been proven valid and useful in other large studies[11, 12]. Subjects reported the average amount of time per week during the past year spent on the following physical activities: running (>10 km/hour), jogging (<10 km/hour), walking outdoors, racquet sports, swimming, cycling, aerobic fitness, other vigorous activities (e.g. vacuum cleaning) and low intensity exercise (e.g. yoga, stretching). A metabolic equivalent (MET) value was assigned to each physical activity following accepted guidelines[13], which allowed for the calculation of the total volume of physical activity. For this purpose, physical activity (in METhours) was calculated by multiplying its associated MET-value by the time (in hours) this physical activity was performed per week. This resulted in a total MET-score for each participant representing the total volume of physical activity. Thereafter, patients were divided into active (50% most active participants, based on baseline MET-score) and inactive participants (50% least active participants) based on median-split to allow for dichotomized analysis.

Clinical events

Clinical events consisted of all-cause mortality and incidence of cerebrovascular events (i.e. a composite endpoint consisting of all TIA's, ischemic strokes, hemorrhagic stroke and vascular dementia). Cerebrovascular events were thereafter divided by cause of stroke (lacunar events (i.e. lacunar TIA and lacunar stroke) and other causes of stroke (e.g. large artery disease or cardio-embolic origin)). All incident events were actively retrieved from patients during follow-up and verified using information from patient records. From participants who were not available for follow-up assessment, medical records were reviewed; in addition, their general practitioner and medical specialists were contacted for information on clinical events and their cognitive status. The onset of clinical events was defined as the date on which the event was diagnosed by either the general practitioner or medical specialist. The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders (IV)[14]. Vascular dementia was based on NINDS-AIREN criteria[15] and probable Alzheimer's disease was based on the NIA-AA criteria[16]. All events were adjudicated by a panel of two neurologists (AMT and FEdL).

MRI protocol

MRI images were acquired at 3 time points (2006, 2011 and 2015) on a 1.5 tesla scanner (2006: Siemens [Munich, Germany], Magnetom Sonata; 2011 and 2015: Siemens, Magnetom Avanto). The protocol included a 3-dimensional T1 magnetization-prepared rapid gradient-echo sequence (voxel size 1.0 X 1.0 X 1.0 mm), a fluid-attenuated inversion recovery (FLAIR) sequence (voxel size 1.0 X 1.2 X 5.0 mm, interslice gap 1.0 mm; follow up: voxel size 1.2 X 1.0 X 2.5 mm, interslice gap 0.5 mm) and a diffusion tensor imaging (DTI) sequence (repetition

time/echo time = 10.100/93 milliseconds; voxel size 2.5 X 2.5 X 2.5 mm). Full acquisition details have been described previously[17].

Assessment of MRI-markers for cSVD.

cSVD was rated according to the Standards for Reporting Vascular Changes on neuroimaging (STRIVE) criteria[7]. The presence of WMHs, lacunes and microbleeds was manually assessed for each patient, which allowed for the generation of an SVD score as previously described[18]. Because periventricular space data was not available, this score is based on the presence of WMHs (with >1 Fazekas score), lacunes and cerebral microbleeds (for each: 0= not present, 1=present). The SVD score therefore had a range from 0 to 3. Additionally, WMH volume was calculated by a semiautomatic segmentation method which has been described in detail elsewhere[19]. Segmentations were visually checked for errors by a trained rater who was blinded to clinical information. Total WMH volume was calculated by summing the segmented areas multiplied by slice thickness. Intracranial volume was determined by summing the total volume of grey matter, white matter and cerebral spinal fluid. Finally, to account for interscan effects, relative WMH volume (adjusted for baseline intracranial volume) was calculated for each individual patient. WMH volume, SVD score and number of microbleeds and lacunes were assessed for each patient in 2006, 2011 and 2015, allowing the determination of changes in these MRI-markers over time.

Assessment of microstructural integrity.

DTI pre-processing was described in detail in a previous article[10]. After pre-processing, the volume-averaged fractional anisotropy (FA) and mean diffusivity (MD) were calculated in the white matter lesions (WMLs) and in normal appearing white matter (NAWM). All images were

visually checked for motion artefacts and co-registration errors. For the DTI analysis, 440 subjects were included after additional exclusion of 63 patients because of excessive motion artefacts or the presence of territorial infarcts. These data were imported into the RUNDMC database and extracted for analysis in 2019.

Statistical analyses

Analyses were performed using RStudio (R Core Team (2019))[20]. All MRI based outcome measures were checked for normality to decide for parametric or non-parametric analyses. Statistical significance was set at $P<0.05$.

To examine the prospective relation between PA and clinical events, we first examined the association between baseline PA and all-cause mortality and incidence of cerebrovascular events using a cox proportional regression analysis. Patients who died were censored. Second, we analysed the cross-sectional relation between baseline PA and MRI-markers of SVD (i.e. SVD score, lacunes, microbleeds, and WMH volume) and white matter microstructure (i.e. MD and FA) with either linear or logistic regression, when appropriate. Third, the association between baseline PA and changes in MRI-markers and white matter microstructure (for each participant) during 9-year follow-up was investigated with linear mixed models. Linear mixed models were performed using the lme4 package[21] with random intercept and an interaction term for group and time to investigate the relation between baseline PA and progression of cSVD.

All statistical analyses were first performed univariate (with only the PA group as independent variable), followed by a multivariate analysis with adjustment for possible confounders at baseline (i.e. age, gender, level of education, normalized total brain volume, executive function, and cardiovascular risk factors (hypertension, body mass index (BMI), diabetes mellitus, use of lipid lowering drugs and smoking status).

Results

Table 1 presents the baseline characteristics of the 503 patients, divided into the physically active and inactive group. Compared to the inactive group, the active group was significantly younger, had a higher total brain volume, had a lower prevalence of hypertension and diabetes, and a lower systolic blood pressure and BMI (table 1). The 9-year follow-up clinical data was available for all patients. Complete MRI data was available for 282 patients (figure 1).

Participants reported a median METhours/week of 97 (IQR: 78-136) and 37 (IQR:22-48) in respectively the active and inactive group. In both groups, the total MET-score decreased significantly across the 9-year follow-up (P<0.001), but total MET-score remained significantly higher in the active group than the inactive group (table 1).

Baseline physical activity and the risk of cerebrovascular events

During 9-year follow-up 92 patients died (32 in the active group vs 60 in the inactive group). A higher baseline PA was independently associated with a lower all-cause mortality (adjusted HR: 0.69, 95%CI: 0.49-0.98, p=0.03) (Figure 2). Furthermore, 74 patients were diagnosed with a cerebrovascular event (26 in the active group vs 48 in the inactive group). A higher baseline PA was independently associated with this composite incidence of all cerebrovascular events (adjusted HR: 0.58, 95%CI: 0.36-0.96, p=0.03). However, when divided into lacunar (n=12 vs 15, HR: 0.83, 95%CI: 0.38-1.83, p=0.65) and non-lacunar events (n=10 vs 18, HR: 0.77, 95%CI: 0.34-1.73, p=0.53), there was no significant association between baseline PA and the risk of the causes of stroke.

Baseline physical activity and MRI-markers for cSVD, at baseline and at follow up

Cross-sectionally the SVD-score was significantly lower in the active group (median: 1 vs 2, p=<0.01), which was mainly due to a lower presence of lacunes in the physically active group (OR: 0.46, 95%CI: 0.30-0.67, p=<0.001). After correction for confounders, this difference disappeared (Table 2). WMH volume at baseline was significantly lower in the active group compared to the inactive group (median: 3.0 ml vs 4.5 ml, p=0.03). However, after adjustment for confounders this association disappeared (Table 2). Finally, with linear mixed models no independent relation was found between PA and the cSVD-related MRI-markers across 9-year follow-up (Table 3). There was no independent association between PA and any of the markers of microstructural integrity, both at the cross-sectional and prospective level (Table 4 and Table 5).

Discussion

We found that higher volumes of baseline PA in patients with cSVD related to a lower all-cause mortality and reduced incidence of all cerebrovascular events compared to patients with a lower baseline PA, across 9-year follow-up. However, we found no such association with lacunar stroke and MRI markers for cSVD.

It is well established that a higher PA can act as an effective strategy for prevention of (progression of) cardiovascular disease in various clinical populations [22-25]. To date, however, the longitudinal association between PA and clinical outcomes and MRI markers of SVD has never been explored in cSVD patients. The long follow-up of 9-years allowed us to detect the clinical impact of baseline PA, which confirmed our hypothesis that higher levels of PA at baseline is strongly associated with better clinical outcome (mortality and cerebrovascular events). This observation fits with the observation that prolonged adherence to high levels of PA is required for clinical benefits[8]. Curiously, we did not find an association between physical

activity and stroke subtype (i.e. lacunar events and other causes of stroke). However, the results of this sub analysis might be underpowered due to the low incidence of these stroke subtypes (27 lacunar events and 28 other causes of stroke respectively). Taken together, our data provide strong support for the relation between high levels of PA and protective clinical benefits in patients with cSVD, even after the diagnosis is made. Contrary to our hypothesis, higher PA volumes were not associated with the (clinical) presentation of cSVD (i.e. lacunar events, MRI-markers of cSVD). Although higher WMH volumes were present in patients with high levels of PA at baseline, this appeared to be confounded by age and total brain volume. Our observations are in contrast with others that report an association between PA and both MRI-markers and microstructural integrity in healthy older adults and cSVD patients[10, 26, 27]. However, these previous studies were cross-sectional, in which reverse causality may have played a role in explaining the observations. The fact that the relation between PA and WMH volume and SVD-score disappeared upon correcting for potential confounders, but also across/over time, highlights the importance to adjust for these factors and to adopt a prospective design. These observations suggest that other factors, independent from PA, may be more important contributors to the progression of MRI markers of cSVD in symptomatic cSVD patients.

Our finding that individuals with higher volumes of PA showed a lower incidence of cerebrovascular events, without affecting markers of cSVD (i.e. lacunar events or MRI markers), raises questions about the potential underlying mechanisms. A frequently discussed explanation for the protective effects of PA on cardiovascular health is that the repeated increase in perfusion of large arteries[28], results in improved cardiovascular health and a lower incidence of cardiovascular disease and all-cause mortality. Several studies have provided strong evidence for a role of perfusion in protecting against clinical events in large and resistance arteries[28]. However, protective mechanisms of the brain (e.g. cerebral autoregulation) seem to limit

increases in cerebral perfusion in small cerebral arteries during exercise.[29] Although previous evidence shows that higher PA is related to an increased cerebral perfusion[30], the relative increase in perfusion of the brain during PA is modest compared to other organs, such as the heart[31-33]. Possibly, this may explain our observation that physical activity protects against cardio- and cerebrovascular morbidity, whilst no protective effects are found in the (small) arteries of the brain. To further investigate this hypothesis studies are required to better understand the causal impact of PA on microvascular perfusion and relate this to clinical outcome

Strengths and limitations.

Strong elements of this study include its large sample size and prospective design. Furthermore, a structured assessment of physical activity and risk factors was used and all associations were corrected for possible confounders which have been described to be strongly related to cSVD progression and brain structure[34]. However, some methodological issues need to be considered. Firstly, due to the observational nature of this study it is impossible to determine a causal relation and therefore results should be considered with caution. To further investigate our promising results, we would recommend to initiate a randomized clinical trial to investigate the causal effects of PA in patients with cSVD. Several early phase trials that incorporate exercise intervention to reduce the progression of cSVD are currently underway[35]. Secondly, although structured questionnaires were used to assess physical activity, the amount of METhours/week reported may not reflect the exact amount of energy expended. Overestimation of PA with the use of questionnaires is a common finding. However, it is still a frequently used, feasible and valid method for the assessment of PA in large sample studies, especially to detect changes over time[36]. Therefore, to be able to make a more reliable distinction between “active” and “inactive” we made the decision to dichotomize the data for our analyses.

Conclusion

Whilst regular physical activity was not related to the progression of MRI markers of cSVD across a 9-year follow-up, results from our study prove that high levels of physical activity in patients with cSVD are associated with a lower all-cause mortality and lower incidence of cerebrovascular events. This work supports the importance for increasing levels of physical activity in the clinical management of cerebrovascular disease, that should first be proven in clinical trials.

Author contributions

TL: Analysis of data, interpretation and writing of the manuscript

DT: Critical revision of the manuscript for important intellectual content

AT: Acquisition of data and analysis

FL: Study concept and design, study supervision and critical revision of the manuscript for important intellectual content

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Disclosures

None

Data Availability Statement

Anonymized data and analytic methods not published in this article will be shared on request with any qualified investigator.

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Figure Legends

Figure 1: Flowchart of the RUNDMC study

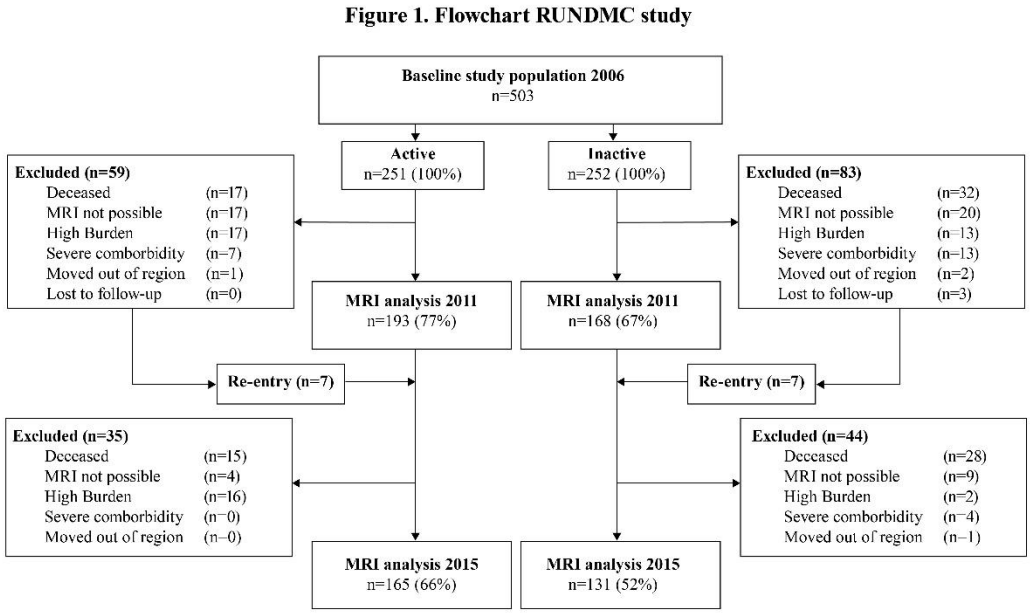
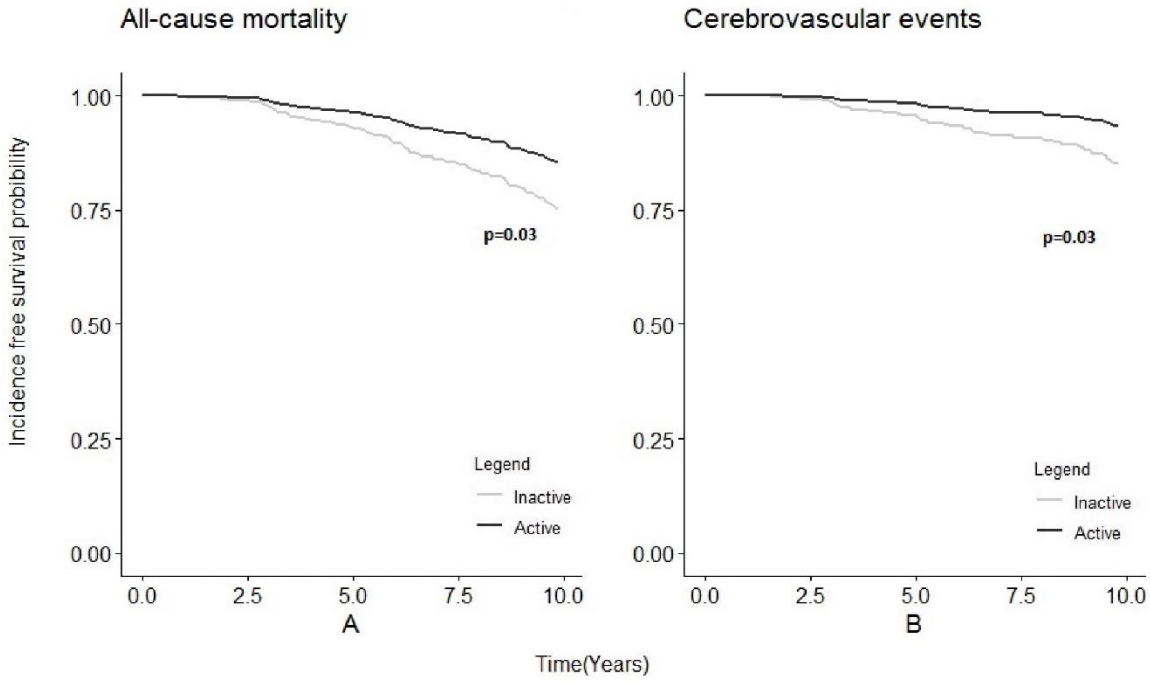


Figure 2: The effect of higher PA on clinical events



Tables

Tables

Table 1. Baseline characteristics

Characteristic	Active (N=251)	Inactive (N=252)	P-value
Age – yr	64.2 (±8.6)	67.0 (±8.7)	<0.001
Male sex	138 (55%)	146 (58%)	0.51
Education†	228 (91%)	226 (90%)	0.66
Total brain volume – ml	1076 (±79)	1046 (±79)	<0.001
Medical history			
Atrial fibrillation	15 (6%)	25 (10%)	0.10
Hypertension	172 (69%)	197 (78%)	0.014
TIA	44 (18%)	60 (24%)	0.08
Ischemic stroke	57 (23%)	56 (22%)	0.90
Hemorrhagic stroke	4 (2%)	4 (2%)	1.00
Myocardial infarction	13 (5%)	22 (9%)	0.12
Diabetes Mellitus	20 (8%)	46 (18%)	0.001
Medication use			
Antihypertensive drugs	117 (47%)	154 (61%)	0.001
Statins	114 (45%)	123 (49%)	0.45
Beta-blockers	81 (32%)	100 (40%)	0.08
Systolic blood pressure – mmHg	138 (±19)	143 (±22)	0.013
Diastolic blood pressure – mmHg	78 (±9)	78 (±10)	0.74
BMI – m/kg^2	26.5 (±4.1)	27.8 (±4.0)	<0.001
Alcohol intake – U/wk	7.3 (8.5)	8.4 (10.0)	0.19
Smoking status			
Never	75 (30%)	74 (29%)	0.90
Former	139 (55%)	140 (55%)	0.56
Active	37 (15%)	38 (15%)	0.92
Executive functioning*	0.06 (±0.75)	-0.07 (±0.77)	0.046
Gaitspeed (m/s)	1.36 (±0.24)	1.18 (±0.32)	<0.001
Total MET-score 2006 – METhours/wk	97 [76-136]	37 [22-48]	<0.001
Total MET-score 2011 – METhours/wk (n=361)	65 [40-96]	34[17-59]	<0.001
Total MET-score 2015 – METhours/wk (n=296)	45 [26-82]	22 [9-40]	<0.001

Values are mean (± standard deviation), number (percentage) or median [interquartile range]. Abbreviations: TIA= Transient ischemic attack BMI = Body mass index; MET=Metabolic equivalent.
† Beyond primary education
* Based on the score of four cognitive tasks (i.e. fluency animals, fluency jobs, STROOP test and verbal series attention task).

Table 2. The effect of physical activity on MRI-markers – cross-sectional

	Univariate			Multivariate		
MRI marker cSVD	β or OR†	95% CI	P-value	β or OR†	95% CI	P-value
WMH volume (ml)	-1.88	-3.35 – -1.06	0.03	-1.05	-1.73 – 1.55	0.82
Microbleeds present	0.76	0.47 – 1.22	0.25	0.88	0.53 – 1.44	0.60
Lacunes present	0.45	0.30 – 0.67	<0.001	0.52	0.33 – 0.81	<0.01
SVD score (0-3)	0.70	0.45 – 0.87	<0.01	0.84	0.54 – 1.11	0.16

The reference group is the inactive group. All multivariate analyses were performed with correction for possible confounders at baseline.

† For WMH volume a β is reported, all other outcomes are odds ratios.

Table 3. The effect of physical activity on MRI-markers – longitudinal

Variable	Fixed effect estimate	95% CI	P-value
WMH volume	-0.04	-2.31 –2.23	0.97
Group*Year 2011	0.13	-1.02 – 1.29	0.82
Group*Year 2015	-0.25	-1.51 –0.99	0.68
Microbleeds (n)	-0.18	-0.77 – 0.41	0.55
Group*Year 2011	0.14	-0.26 – 0.53	0.50
Group*Year 2015	-0.14	-0.58 – 0.29	0.52
Lacunes (n)	-0.18	-0.42 – 0.05	0.14
Group*Year 2011	-0.02	-0.15 – 0.11	0.76
Group*Year 2015	-0.17	-0.32 – -0.03	0.02
SVD score (0-3)	-0.13	-0.28 – 0.03	0.12
Group*Year 2011	0.04	-0.05 – 0.13	0.38
Group*Year 2015	-0.04	-0.14 – 0.06	0.44

The reference group is the inactive group. All statistical analyses were performed with correction for possible confounders at baseline.

Table 4. The effect of physical activity on microstructural integrity – cross-sectional

	Univariate			Multivariate		
Parameter	β	95% CI	P-value	β	95% CI	P-value
MD in WMLs (*10^{-3})	-13.7	-32.2 – 4.82	0.15	-10.6	-28.7 – 7.40	0.25
MD in NAWM (*10^{-3})	-6.72	-15.9 – 2.54	0.15	-5.02	-11.7 – 1.62	0.14
FA in WMLs (*10^{-3})	-2.01	-11.5 – 7.49	0.68	-3.63	-13.2 – 5.93	0.46
FA in NAWM (*10^{-3})	4.77	0.48 – 9.05	0.03	3.55	-0.55 – 7.64	0.09

The reference group is the inactive group. All multivariate analyses were performed with correction for possible confounders at baseline.

Table 5. The effect of physical activity on microstructural integrity – longitudinal

Variable	Fixed effect estimate	95% CI	P-value
MD in WMLs	-0.01	-0.03 – 0.01	0.35
Group*Year 2011	0.001	-0.03 – 0.03	0.94
Group*Year 2015	-0.0005	-0.03 – 0.03	0.97
MD in NAWM	-0.005	-0.015 – 0.005	0.32
Group*Year 2011	0.0008	-0.011 – 0.012	0.88
Group*Year 2015	0.004	-0.007 – 0.016	0.43
FA in WMLs	-0.003	-0.013 – 0.007	0.60
Group*Year 2011	0.001	-0.010 – 0.012	0.82
Group*Year 2015	0.002	-0.008 – 0.014	0.63
FA in NAWM	0.003	-0.005 – 0.012	0.43
Group*Year 2011	-0.0007	-0.011 – 0.010	0.88
Group*Year 2015	-0.0002	-0.010 – 0.010	0.97

The reference group is the inactive group. All statistical analyses were performed with correction for possible confounders at baseline.