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Physical Activity and Brain Health in Patients with Atrial Fibrillation

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Short title: Physical Activity and Brain Health

Word count: 3517

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.15660

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Keywords: Cognitive disorders and dementia, cerebral infarction, Atrial fibrillation, physical activity, neurocognitive function, cerebral microbleeds, total brain volume, white matter disease

Abstract

Background

Vascular brain lesions, such as ischemic infarcts, are common among patients with atrial fibrillation (AF) and are associated with impaired cognitive function. The role of physical activity in the prevalence of brain lesions and cognition in AF has not been investigated.

Methods

Patients from the multicenter Swiss-AF cohort study were included in this cross-sectional analysis. We assessed regular exercise (at least once weekly) and minutes of weekly physical activity using a validated questionnaire. We studied associations with ischemic infarcts, white matter hyperintensities, cerebral microbleeds, and brain volume on brain MRI and with global cognition measured with a cognitive construct score (CoCo).

Results

Among 1490 participants (mean age 72 ±9 years), 730 (49%) engaged in regular exercise. In adjusted regression analyses, regular exercise was associated with a lower prevalence of ischemic infarcts (odds ratio [OR]) 0.78, 95% CI 0.63-0.98, p=0.03) and of moderate to severe white matter hyperintensities (OR 0.78, 95% CI 0.62-0.99, p=0.04), higher brain volume (β-coefficient 10.73, 95% CI 2.37-19.09, p=0.01), and higher CoCo score (β-coefficient 0.08, 95% CI 0.03-0.12, p<0.001). Increasing weekly physical activity was associated with higher brain volume (β-coefficient 1.40, 95% CI 0.65-2.15, p<0.001).

Conclusion

In AF patients, regular exercise was associated with a lower prevalence of ischemic infarcts, of moderate to severe white matter disease, with larger brain volume and better cognitive performance. Prospective studies are needed to investigate if these associations are causal. Until

then, our findings suggest that patients with AF should be encouraged to remain physically active.

Introduction

The prevalence and incidence of atrial fibrillation (AF) is increasing globally.[1, 2] Lifetime risk of AF was 1 in 3 among white women and men in the ARIC cohort in the United States and 1 in 5 among African Americans.[3]

Cognitive impairment is a global health concern and emerging evidence indicates that AF is associated with cognitive decline and dementia.[4-6] The increased risk of stroke in AF patients partially explains this association, but covert brain infarcts and other mechanisms may cause cognitive impairment among AF patients without a history of clinically manifest stroke.[5-7] Covert brain lesions may be of cardioembolic origin, but may also occur due to concomitant large artery or small vessel disease owing to shared vascular risk factors.

Treatment of covert brain lesions like WMHs of presumed vascular origin is currently limited to preventive lifestyle modifications and risk factor management.[8] In previous studies, physical activity (PA) was reported to be associated with reduced risk of coronary heart disease, ischemic stroke, and total cardiovascular disease in older adults. [9] Accordingly, increasing PA in late-life is assumed to promote cerebral small vein integrity.[10] Physical inactivity has been associated with increased risk for dementia in older individuals[11] and poor performance on neurocognitive tests.[12] Regular leisure time PA, on the other hand, has been associated with reduced risk of dementia or Alzheimer's disease in longitudinal studies.[13, 14] Additionally, PA has been associated with a larger brain volume in older adults.[15] However, a number of studies have not been able to confirm an association between PA and brain volume, WMH volume or hippocampal volume.[16-18] Whether PA may have a beneficial effect on covert brain lesions and cognitive performance in patients with AF has yet to be explored. The aim of the present study was to investigate the association

between PA and vascular brain lesions, brain volume and cognition in an elderly Swiss cohort of AF patients.

Methods

Study design and patient population

This was a cross-sectional analysis of patients participating in the Swiss-AF study (Swiss Atrial Fibrillation Cohort; ClinicalTrials.gov Identifier: NCT02105844), an ongoing, prospective, multicentric study in Switzerland, including German, French and Italian speaking regions. One of the main aims of Swiss-AF is to investigate the association of AF with cognitive decline and dementia.[19] A total of 2415 patients with documented AF and ≥65 years, including a subgroup of approximately 10 percent of patients <65 years to assess socioeconomic aspects, were recruited between 2014 and 2017. Exclusion criteria were the inability to provide informed consent, exclusively non-sustained episodes of AF due to reversible causes, or any acute illness (including stroke or TIA) within 4 weeks before inclusion.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol adheres to the Declaration of Helsinki and has been approved by the local ethics committee EKNZ (Ethikkommission Nordwest- und Zentralschweiz). Written informed consent was signed by each participant.

Data Availability

Data supporting the findings of this study and any data not published within this article is accessible in a public repository. On request, data are available from the corresponding author.

Data Acquisition

Questionnaires were used to assess demographic information including age, sex, and education level. Education levels were classified as basic (≤6 years), middle (>6 years and ≤12 years), and advanced (>12 years of education). Weight and height was asked to determine body mass index (kg/m^2). Smoking status was classified as active, past, or never. Alcohol intake was assessed as

average drinks per day. A self-perception score from 0-100 was used to assess the patients' current impression concerning their overall state of health. Zero represents the worst, and 100 represents the best imaginable state of health. Medical history, risk factors and medication including anticoagulation were asked to evaluate medical conditions. The CHA_2DS_2-VASc score was calculated subsequently. The AF type was divided into paroxysmal (self-terminating, <7 days), persistent (≥7 days and/or requiring cardioversion), and permanent AF (unsuccessful cardioversion or no attempt to terminate AF). Blood pressure was measured in supine position at study enrollment.[19]

Assessment of exercise and physical activity

PA was assessed by questionnaires, firstly asking if participants engaged in regular physical exercise, listing jogging, nordic walking, cycling, aerobics or ball sports as examples. Regular exercise (RE) was defined as performing such activities at least once per week. The choice of this cut-off was arbitrary and informed by the distribution of PA in our study population, yielding patient groups of comparable size.

The quantity and intensity of weekly PA was reported using the validated International Physical Activity Questionnaire (IPAQ),[20, 21] which assesses the amount of weekly "vigorous" (making one breathe much harder than normal) and "moderate" (making one breathe somewhat harder than normal) physical activity, as well as walking (including any walking, at work, at home or during leisure time). As a quantitative measure of weekly physical activity, we calculated the metabolic equivalent of task (MET)-minutes per week as an index of energy expenditure based on the information gathered with the IPAQ (MET-min/week). Additionally, we adapted the MET intensity by age according to the American College of Sports Medicine (MET-min/week age adapted).[22] For middle-aged participants (40-64 years) the following factors as mean of the corresponding range were used: walking = 2.95 METs, moderate intensity = 4.95 METs, vigorous intensity 7.2 METs. For older participants (≥65 years) walking = 2.35 METs, moderate intensity = 3.95 METs and vigorous intensity = 5.75 METs were used. The reason for using age-adapted MET-values was recent evidence showing that absolute intensity cut-offs may lead to false classification of PA in populations other than those the cut-offs were derived from.[23]

Brain magnetic resonance imaging (bMRI) and brain lesions

A standardized bMRI protocol without contrast agent was run in AF patients without contraindications (cardiac device, claustrophobia). Images were evaluated by trained neuroradiologists in the Medical Image Analysis Centre (MIAC AG) Basel. MRIs were assessed without knowledge of the patients' physical activity. The following lesions were discerned, as previously described:[6] *Large non-cortical and cortical infarcts (LNCCIs)* included cortical infarcts defined as hyperintense lesions on FLAIR involving the cortex irrespective of their size and whether or not they also involve subcortical areas and non-cortical lesions with a diameter >20mm.[6] *Small non-cortical infarcts (SNCIs)* consist of hyperintense lesions on FLAIR ≤20mm in diameter on axial sections a not involving the cortex, consistent with ischemic infarction in the territory of a perforating arteriole (located in the white matter, internal or external capsule, deep brain nuclei, thalamus, or brainstem).[6] For this specific analysis, we combined the prevalence and volume of LNCCIs and SNCIs and analyzed them together as any ischemic infarct. *White matter hyperintensities (WMH)*[24] of presumed vascular origin were identified and graded on FLAIR images using the Fazekas scale. Moderate to severe WMH was defined as a score ≥2 in either the periventricular or the deep white matter region. *Cerebral microbleeds (CMB)*[24] were identified as round, small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.[6] The *normalized brain volume (nBV)* was estimated in milliliters on 3D T1-weighted MPRAGE images using SIENAX and normalized for skull size.[25]

Neurocognitive function

The following neurocognitive tests were performed by trained study personnel in a standardized manner according to the study protocol: *Montreal Cognitive Assessment (MoCA)* which evaluates memory, visuospatial abilities, executive functions, phonemic fluency, attention, concentration, confrontation naming, abstraction and orientation.[26] *Trail Making Test (TMT)* which assesses visual attention, processing speed and executive functions. The test consists of connecting numbers in ascending order (TMT-A) and connecting numbers and letters alternating in ascending or alphabetic order, respectively (TMT-B).[27] *Semantic Fluency Test (SFT)* is testing for

semantic memory and language production, for which patients are asked to name as many animals as possible within 1 minute.[28] *Digit Symbol Substitution Test (DSST)* explores cognitive aspects such as information processing speed, visuomotor coordination and attention.[19] *The Cognitive Cognitive Construct Score (CoCo)* is a score previously derived from the individual components of all neurocognitive tests performed in Swiss-AF (MoCA, TMT, SFT, DSST) using latent factor analysis and summarizes global cognitive performance.[29]

Statistical analysis

The baseline characteristics were displayed overall and stratified by RE (yes or no). Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical data is presented as absolute and relative frequencies.

The associations between RE as a binary variable and the prevalence of ischemic infarcts, CMB and moderate to severe WMH as outcome variables were investigated with multivariable adjusted logistic regression models. We used multivariable adjusted linear regression models to evaluate the association of RE with total brain volume and cognition. Age-adapted MET-minutes per week were used as a quantitative measure of PA, both as a continuous variable (per 1000 MET-min/week) as well as a categorical variable using quartiles. P-value for linear trend was calculated to describe the shape of the association. Results are presented as odds ratio (OR) or β-coefficients, 95% confidence intervals (CI) and p-values, with a p-value below 0.05 indicating statistical significance.

Various adjustments were done: model 1 was unadjusted, model 2 was adjusted for age and sex, and model 3 was additionally adjusted for smoking status, AF type (paroxysmal vs non paroxysmal), hypertension, diabetes mellitus, heart failure, coronary heart disease, statin therapy, antihypertensive medication, oral anticoagulation and antiplatelet therapy. In addition to these variables, the regression analysis using neurocognitive function as the outcome was adjusted for education (models 1-3) and for the presence of ischemic infarcts or moderate to severe WMH ≥2 (model 3). As a sensitivity analysis, all analyses were repeated excluding patients with a history of stroke or TIA. Additionally, the CoCo score stratified by regular exercise was calculated for the

following age strata: ≤60, 61-70, 71-80, >80 years. To assess how well the results from this analytic sample apply to the complete study sample, we compared the baseline characteristics of included Swiss-AF patients with those who were excluded from the present analysis. The statistical analysis was performed using R (Version 4.1.0).

Results

A total of 1490 patients with brain MRI, available data on PA and neurocognitive function were included (Figure S1). The most common reason for exclusion was lack of a brain MRI. Mean age was 72 ± 9 years and 392 patients (26%) were female. Most patients had paroxysmal AF (690, 46%), 461 patients (31%) had persistent and 339 (23%) had permanent AF. Almost half of the participants reported engaging in regular exercise (RE, 730, 49%). Patients doing RE achieved a median of 4343 age-adapted MET-minutes per week (IQR 2195-7862), whereas patients without RE activities achieved a median of 2540 age-adapted MET-minutes per week (IQR 987-6389). Patients doing RE were younger, tended to have fewer cardiovascular risk factors such as diabetes or hypertension, less cardiovascular medication, and had higher education as those who did not report RE (Table 1). The mean CHA_2DS_2-VASc score of the entire analysis population was 3.2 ± 1.7.

Participants in Swiss-AF who were excluded from this analysis were older (74.4 vs. 72.3 years), had more medical risk factors (CHA2DS2-VASc score 3.8 vs. 3.2), more cardiovascular medication, lower health perception scores and less physical activity than the patients included in this analysis. The differences in patient characteristics according to regular exercise were similar to the included patients (Table S4).

Table 2 presents the prevalence and volume of vascular brain lesions on MRI stratified by RE. Overall, patients reporting RE had less often ischemic infarcts (244 [33%] vs. 317 [42%]), cerebral microbleeds (136 [19%] vs. 178 [24%]) and moderate to severe WMH (347 [48%] vs. 437 [58%]) than those not engaging in RE (Figure 1).

Table 3 shows the association of RE and weekly PA (quantified in MET-min/week) with the presence of vascular brain lesions on MRI in all 3 models. Patients engaging in RE had significantly lower odds of having ischemic infarcts (OR 0.78, 95% CI 0.63-0.98, p = 0.03), and moderate to severe WMH (OR 0.78, 95% CI 0.62–0.99, p = 0.04), even after adjustment for cardiovascular risk factors (model 3). There was no association between RE and the presence of cerebral microbleeds. Weekly PA was inversely associated with the presence of cerebral

microbleeds (model 3; OR 0.95, 95% CI 0.92-0.98, p < 0.001 per 1000 MET-minutes per week). This association followed a linear trend (p for linear trend = 0.002). There were no significant associations between weekly PA and the presence of ischemic infarcts and moderate to severe WMH in the adjusted logistic regression models (model 2 and 3).

The sensitivity analysis excluding patients with history of stroke or TIA is shown in Table S2 (n=1204) and showed consistent results compared to the main analysis.

Both, total brain volume (median 1430 ml [IQR 1365-1493] vs. 1400 ml [IQR 1347-1466]) and global cognitive performance CoCo score (median 0.14 [IQR -0.19-0.48] vs. -0.09 [IQR -0.43-0.30]) were higher in patients reporting RE (Figure 2). The CoCo score was higher among patients reporting RE in each age stratum (Figure S2).

Table 4 shows the association of RE and PA with total brain volume and cognitive function. RE as well as weekly PA were strongly associated with normalized brain volume. Weekly MET-minutes followed a linear trend showing more activity was associated with higher brain volume (p for linear trend <0.001). Patients reporting RE had significantly higher CoCo scores, also when adjusted for education, cardiovascular risk factors and the presence of brain infarcts (model 3; β-coefficient 0.08, 95% CI 0.03–0.12, p < 0.001).

Discussion

This cross-sectional analysis revealed several potentially important findings on PA and brain health in patients with AF. First, patients engaging in RE less often had ischemic brain infarcts or moderate to severe white matter disease on MRI. Second, higher intensity and quantity of PA was inversely associated with the prevalence of cerebral microbleeds. Third, patients engaging in RE and being physically more active had larger normalized brain volumes. Fourth, patients reporting RE performed better in cognitive tests.

From a physiological perspective, exercise may promote 'brain health' by altering mechanisms of neuronal plasticity and supporting the brain's structural integrity and function.[30] Neuroprotective mechanisms of exercise can be explained with improved cerebrovascular angiogenesis and neurogenesis, reduced neuronal apoptosis, altered inflammatory response, and higher antioxidant capacity.[30, 31] Higher antioxidant capacity leads to an increased ischemic tolerance of brain tissue.[31] Previous small studies demonstrated that PA was associated with a lower burden of neuroimaging lesions of presumed vascular origin in older adults.[10] Covert brain infarcts are common among patients with AF,[4, 6] but the evidence to what extent patients with AF might benefit from PA has been limited. Escudero-Martínez et al. found that a high level of PA combined with good adherence to a Mediterranean diet was associated with a lower risk of silent brain infarcts in patients with AF.[32] No independent association of PA and risk reduction of silent brain infarcts was found, but this may have been due to the relatively small sample size of 443 patients and lack of power.[32] We were conscious about potential confounding by reverse causation, as patients who suffered a stroke are both less able to engage in physical activities and more likely to have brain infarcts on MRI. Therefore, we performed a sensitivity analysis excluding patients with a history of stroke or TIA and found essentially the same effect of PA on covert brain infarcts, in line with previous studies in the general population.[9, 31, 33]

We combined brain infarcts of possible embolic origin (LNCCI) and those presumably caused by small vessel disease in our analysis, chiefly for reasons of power. Thus, we cannot speculate about possible mechanisms by which PA might prevent cerebral infarcts in patients with AF. Of

note, the association persisted after adjustment for numerous vascular risk factors, suggesting that the protective effect of PA is at least in part independent of those.

White matter hyperintensities (WMH) and cerebral microbleeds (CMB) are generally considered markers of cerebral small vessel disease.[24, 34] WMH are associated with an increased risk of stroke, cognitive impairment and vascular dementia.[6, 35] Among patients with cerebral small vessel disease, PA has been associated with a lower all-cause mortality and lower incidence of cerebrovascular events, although no correlation with WMH or CMB was found.[36] Resistance training has been reported to reduce WMH progression in a randomized controlled trial.[37] In a systematic review, higher levels of PA were associated with greater white matter volumes, reduced volume or severity of WMH, or improved measures of white matter microstructure.[18] Our study expanded these findings to patients with AF by demonstrating a lower prevalence of moderate to severe WMH among patients with engaging in RE, after adjustment for vascular risk factors.

Patients with CMB are at increased risk for intracranial haemorrhage, which is especially relevant for patients requiring long-term anticoagulation.[38, 39] Our findings relating to the effect of PA on CMB were less conclusive: while RE was associated with a lower likelihood of cerebral microbleeds, the association was weakened after adjustment for vascular risk factors. In contrast, weekly PA quantified by MET-minutes showed an inverse linear relationship with the presence of CMB, even in the full multivariate model. One might speculate that only relatively high intensities of PA protect against cerebral microbleeds.

The association of PA with larger brain volume, better cognitive function, and lower risk for dementia in the general population, including the elderly, has already been established.[11, 40] Aerobic exercise training has been shown to be effective at reversing hippocampal volume loss in late adulthood, which is accompanied by improved memory function.[41] Progressive aerobic training has also been found to improve cognitive function in a randomized controlled trial.[42] In our study, RE and higher weekly PA were associated with larger normalized brain volume. Although regional volumes relevant for memory function were not available for the present

analysis, we were able to show that RE and, by trend also weekly PA, were independently associated with better global cognitive performance. In a post-hoc analysis, RE was associated with better cognitive performance in all age strata. Thus, PA might reduce brain atrophy and improve cognitive function in patients with AF.[30]

Additionally, the risk of falls has to be considered, especially among elderly patients on oral anticoagulation. However, exercise programs have been shown to reduce falls in older people.[43] Accordingly, physical activity can also be seen as a preventive measure to reduce the risk of falls, although further studies are needed especially on which type of physical activity is safe and most favorable in this regard in the elderly.

The amount of physical activity in our study population (median 4479 MET-min/week) is somewhat lower than in the general Swiss population >65 years (mean 5692 in people aged > 65 years).[21] However, this difference can be expected as we included patients with heart disease.

Strengths and Limitations

There are several strengths of this study. First, the sample size is large and consists of well-characterized patients with AF. As we have detailed data on patients' characteristics and medical history, we were able to adjust for several potential confounders. Second, brain MRI scans were performed according to a standardized protocol and analyzed by trained neuroradiologists. Third, study personnel were trained to perform neurocognitive tests in a consistent way in order to ensure comparability and minimize performance bias. Fourth, the IPAQ is a well-validated questionnaire allowing comparison with other studies and research data.

The most important limitation of the present analysis is its cross-sectional design, which does not allow establishing a causal relationship between PA and the outcomes measured. Prospective trials are needed to explore whether PA prevents vascular brain lesions and cognitive decline. There are far more males in our study population than females. Male sex is a known risk factor for AF.[44] Even when taking into consideration that more men than women live with cardiovascular disease,[45] women are still underrepresented in cardiovascular research, possibly due to reduced willingness to participate, sociocultural factors, and lack of awareness on the part of investigators.[46] As we did not keep a screening log of subjects declining to participate in Swiss-AF, we cannot provide specific reasons for under-representation of women in our study.

Furthermore, the questionnaire was completed by the study patients without supervision. Examples were given for each PA level but a wide range of individual interpretation is possible. Moreover, we cannot draw any conclusions as to the optimal quantity or intensity of PA, as the analysis of MET-minutes per week did not yield consistent linear effects, except on brain volume.

Finally, although we adjusted for several potential confounders, we cannot rule out residual confounding through non-measured factors or behaviors associated with a healthy lifestyle.

Conclusion

A majority of research in lifestyle interventions focuses on healthy older adults. The present study examined the potential importance of physical activity for brain health in patients with AF. The main conclusion is that the beneficial effects of physical activity on brain health may also be present in patients with atrial fibrillation. The associations with a lower prevalence of ischemic brain infarcts and white matter disease, larger brain volume, as well as better neurocognitive performance might indicate potential protective effect of PA, but confirmation in prospective studies is warranted. Pending further research, patients with AF can be encouraged to remain physically active.

Funding

The Swiss-AF study is supported by grants of the Swiss National Science Foundation (grant numbers 33CS30_148474, 33CS30_177520, 32473B_176178, and 32003B_197524), the Swiss Heart Foundation, the Foundation for Cardiovascular Research Basel (FCVR), and the University of Basel.

Disclosures

E. Herber reports no disclosures; **S. Aeschbacher** reports no disclosures; **M. Coslovsky** reports no disclosures; **F. Schwendinger** reports no disclosures; **E. Hennings** reports no disclosures; **A. Gasser** reports no disclosures; **M. Di Valentino** reports no disclosures; **E. Rigamonti** reports no disclosures; **T. Reichlin** has received research grants from the Goldschmidt-Jacobson Foundation, the Swiss National Science Foundation, the Swiss Heart Foundation, the European Union, the Professor Max Cloëtta Foundation, the Cardiovascular Research Foundation Basel, the University of Basel and the University Hospital Basel, all outside of the presented work. He has received speaker/consulting honoraria or travel support from Abbott/SJM, Astra Zeneca, Brahms, Bayer, Biosense-Webster, Medtronic, Pfizer-BMS and Roche, all outside of the presented work. He has received support for his institution's fellowship program (Inselspital Bern) from Biosense-Webster, Biotronik, Medtronic, Abbott/SJM and Boston Scientific, all outside of the presented work; **N. Rodondi** received a grant from the Swiss Heart Foundation; **S. Netzer** reports no disclosures; **J. H. Beer** reports grants from the Swiss National Foundation of Science, The Swiss Heart Foundation, grants from Bayer, lecture fees from Sanofi Aventis and Amgen, to the institution outside the submitted work; **A. Stauber** reports no disclosures; **A. Müller** has received fellowship and training support from Biotronik, Boston Scientific, Medtronic, Abbott/St. Jude Medical, and Biosense Webster, and speaker honoraria from Biosense Webster, Medtronic, Abbott/St. Jude Medical, AstraZeneca, Daiichi Sankyo, Biotronik, MicroPort and is a consultant for Biosense Webster, Medtronic, and Abbott/St. Jude Medcal; **P. Ammann** reports no disclosures; **T. Sinnecker** reports no disclosures; **M. Duering** is an employee of MIAC AG, has received speaker honoriaria from Bayer Vital and Sanofi Genyzme and is a consultant for Hovid Berhad and Roche Pharma, all outside of the presented work; **J. Wuerfel** is an employee of MIAC AG, has received funding from EU (Horizon2020), Else-Kröner-Fresenius Foundation, Novartis Foundation, and consultancy, steering committee, advisory board and speaker honoraria from Actelion, Bayer, Biogen, Idorsia, Roche, Sanofi-Genzyme and Teva; **D. Conen** received speaker fees from BMS/Pfizer, and consulting fees from Roche Diagnostics, both outside of the current work; **M. Kühne** reports personal fees from Bayer, personal fees from Böhringer Ingelheim, personal fees from Pfizer BMS, personal fees from Daiichi Sankyo, personal fees from Medtronic, personal fees from Biotronik, personal fees from Boston Scientific, personal fees from Johnson&Johnson, personal fees from Roche, grants from Bayer, grants from Pfizer, grants from Boston Scientific, grants from BMS, grants from Biotronik, grants from Daiichi Sankyo; **S. Osswald** received a grant from the Swiss National Science Foundation; **L. H. Bonati** received grants from

the Swiss National Science Foundation (PBBSB-116873, 33CM30-124119, 32003B-156658, 32003B-197524); Berne, Switzerland), The Swiss Heart Foundation (Berne, Switzerland, and the University of Basel (Basel, Switzerland). LHB has received an unrestricted research grant from AstraZeneca, and consultancy or advisory board fees or speaker's honoraria from Amgen, Bayer, Bristol-Myers Squibb, and Claret Medical, and travel grants from AstraZeneca and Bayer.

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Figure legend

Figure 1: Prevalence (%) of vascular brain lesions stratified by regular exercise

The bar chart shows the prevalence of ischemic infarcts, microbleeds and white matter disease as relative frequencies and stratified by regular exercise. RE = regular exercise; PA = physical activity. P values are adjusted for age, sex, smoking status, AF type (paroxysmal vs non paroxysmal), hypertension, diabetes mellitus, heart failure, coronary heart disease, statin therapy, antihypertensive medication, oral anticoagulation and antiplatelet therapy.

Figure 2: Total brain volume (ml) and cognitive construct (CoCo) score stratified by regular exercise

The violin plot shows the distribution of total brain volume (regular exercise yes: median 1430 ml [IQR 1365-1493]; regular exercise no: median 1400 ml [IQR 1347-1466]) and the cognitive construct (CoCo) score (regular exercise yes: median 0.14 [IQR -0.19-0.48]; regular exercise no: median -0.09 [IQR -0.43-0.30]) compared between Swiss-AF participants doing regular exercise or not. The box illustrates the range between the first and third quartile, the median is shown as line splitting the box and the cross indicates the mean. IQR = interquartile range.

Table 1: Baseline characteristics overall and stratified by regular exercise

Characteristic	Overall	Regular exercise		p-value
		Yes	No	
n (%)	1490	730 (49.0)	760 (51.0)	
Age, y (mean, SD)	72.3 (8.5)	71.5 (8.0)	73.2 (8.9)	<0.001
Female sex, n (%)	392 (26.3)	189 (25.9)	203 (26.7)	0.76
Education level, n (%)				<0.001
Basic	162 (10.9)	55 (7.5)	107 (14.1)	
Middle	739 (49.6)	329 (45.1)	410 (53.9)	
Advanced	588 (39.5)	345 (47.3)	243 (32.0)	
Body mass index, kg/m^2 (mean, SD)	27.6 (4.7)	27.1 (4.3)	28.1 (4.9)	<0.001
Blood pressure (systolic/diastolic mmHg) (mean, SD)	134/78 (19/12)	134/79 (18/11)	135/77 (19/13)	0.90/0.002
Smoking status, n (%)				0.007
Active	112 (7.5)	45 (6.2)	67 (8.8)	
Past	724 (48.6)	337 (46.2)	387 (50.9)	
Never	654 (43.9)	348 (47.7)	306 (40.3)	
Average alcohol intake (drinks/day) (median [IQR])	0.50 [0.1, 1.3]	0.57 [0.1, 1.3]	0.50 [0.1, 1.3]	0.04
Health perception score (0-100) (median [IQR])	80.0 [65.0, 85.0]	80.0 [70.0, 90.0]	74.5 [60.0, 80.0]	<0.001
Atrial fibrillation type, n (%)				0.11
Paroxysmal	690 (46.3)	342 (46.8)	348 (45.8)	
Persistent	461 (30.9)	238 (32.6)	223 (29.3)	
Permanent	339 (22.8)	150 (20.5)	189 (24.9)	
CHA_2DS_2-VASc score (mean, SD)	3.2 (1.7)	3.0 (1.7)	3.4 (1.8)	<0.001

Medical history, n (%)				
Diabetes	212 (14.2)	70 (9.6)	142 (18.7)	<0.001
Hypertension	1016 (68.2)	468 (64.1)	548 (72.1)	0.001
Heart failure	318 (21.4)	130 (17.8)	188 (24.8)	0.001
Coronary artery disease	411 (27.6)	195 (26.7)	216 (28.4)	0.50
Clinical stroke	186 (12.5)	84 (11.5)	102 (13.4)	0.30
TIA	135 (9.1)	58 (7.9)	77 (10.1)	0.17
Major bleeding	79 (5.3)	29 (4.0)	50 (6.6)	0.03
Renal failure	263 (17.7)	121 (16.6)	142 (18.7)	0.32
Cardiovascular medication, n (%)				
Antihypertensive drugs*	1301 (87.3)	606 (83.0)	695 (91.4)	<0.001
Betablocker	1027 (68.9)	489 (67.0)	538 (70.8)	0.13
ACE-Inhibitors	439 (29.5)	199 (27.3)	240 (31.6)	0.08
Angiotensin receptor blockers	453 (30.4)	219 (30.0)	234 (30.8)	0.78
Digoxin	72 (4.8)	32 (4.4)	40 (5.3)	0.50
Diuretics	618 (41.5)	248 (34.0)	370 (48.7)	<0.001
Statin therapy (hypercholesterolemia)	714 (47.9)	332 (45.5)	382 (50.3)	0.07
Antiarrhythmics class Ic and III	312 (20.9)	144 (19.7)	168 (22.1)	0.29
Oral anticoagulation intake, n (%)	1339 (89.9)	659 (90.3)	680 (89.5)	0.67
NOAC	788 (52.9)	395 (54.1)	393 (51.7)	0.38
Vitamin K antagonist	551 (37.0)	264 (36.2)	287 (37.8)	0.56
Antiplatelet therapy (including Aspirin)	268 (18.0)	117 (16.0)	151 (19.9)	0.06
Physical activity (MET-min/week [IQR])	4479 [1780, 8943]	5466 [2772, 9583]	3193 [1342, 7899]	<0.001
Physical activity (MET-min/week age-adapted; median [IQR])	3633 [1418, 7266]	4343 [2195, 7862]	2540 [987, 6389]	<0.001

Values presented as mean ± SD, median (interquartile range) or n (%). Education levels were defined as basic: ≤ 6 years, middle: > 6 years and ≤ 12 years, and advanced: > 12 years of education. CHA_2DS_2-VASc score = heart failure, hypertension, age ≥75 years (2 points), diabetes, history of stroke, TIA or thromboembolism (2 points), vascular disease, age ≥65 and <75 years, female sex. Health perception score is a self-assessment concerning the participants' current state of health on a scale from 0-100. ACE = angiotensin converting enzyme; IQR = interquartile range; MET = metabolic equivalent of task; NOAC = new oral anticoagulants; SD = standard deviation; TIA = transient ischemic attack.

*antihypertensive drugs include angiotensin-converting-enzyme inhibitors, beta blockers, angiotensin-1-receptor-blockers, calcium antagonists, diuretics, renin antagonists, aldosterone antagonists.

Missing values: blood pressure (n=6), heart failure (n=1), Renal failure (n=1), education level (n=1).

Table 2: Prevalence and volume of brain lesions detected on bMRI stratified by regular exercise

All patients (n = 1490)	Overall	Regular exercise	
		Yes	No
Any ischemic infarct (LNCCI and SNCI)			
Prevalence (n, %)	561 (37.7)	244 (33.4)	317 (41.7)
Volume (median [IQR]) (mm3)	285 [69, 2361]	279 [66, 3317]	288 [75, 2223]
Cerebral microbleeds (CMB)			
Prevalence (n, %)	314 (21.7)	136 (19.3)	178 (24.1)
Counts (median [IQR])	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
White matter hyperintensities (WMH)			
Prevalence (n, %), Fazekas scale ≥2	784 (52.7)	347 (47.5)	437 (57.6)
Volume (median [IQR]) (mm3)	3756 [1368, 9480]	3177 [1242, 7830]	4172 [1562, 10803]

Values are median [interquartile range] or n (%). Only the volume of patients showing presence of lesions was taken into account. Missing values: cerebral microbleeds count (n=46), white matter hyperintensities (n=1).

bMRI = brain magnetic resonance imaging; IQR = interquartile range; LNCCI = large noncortical and cortical infarcts (including acute lesions); SNCI = small noncortical infarcts (including acute lesions).

Table 3: Association of regular exercise and weekly physical activity with the prevalence of brain lesions

All patients (n = 1490)	Model 1	Model 2	Model 3
	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value
Any ischemic infarct			
Regular exercise (yes/no)	0.70 (0.57-0.87) <0.001	0.77 (0.62-0.96) 0.02	0.78 (0.63-0.98) 0.03
Physical activity (per 1000 MET-min/week)	0.97 (0.95-0.99) 0.003	0.99 (0.97-1.01) 0.48	0.99 (0.97-1.01) 0.52
Q1: <1417 MET-min/week	Ref	Ref	Ref
Q2: 1417-3634 MET-min/week	0.87 (0.65-1.16) 0.33	0.89 (0.66-1.20) 0.44	0.88 (0.65-1.20) 0.43
Q3: 3635-7265 MET-min/week	0.79 (0.59-1.06) 0.12	0.83 (0.61-1.13) 0.24	0.82 (0.60-1.11) 0.20
Q4: >7265 MET-min/week	0.63 (0.47-0.85) 0.002	0.80 (0.59-1.10) 0.17	0.81 (0.59-1.11) 0.20
P for linear trend	0.002	0.16	0.17
Cerebral microbleeds			
Regular exercise (yes/no)	0.76 (0.59-0.97) 0.03	0.82 (0.63-1.06) 0.13	0.86 (0.66-1.11) 0.24
Physical activity (per 1000 MET-min/week)	0.94 (0.91-0.96) <0.001	0.95 (0.92-0.98) <0.001	0.95 (0.92-0.98) <0.001
Q1: <1417 MET-min/week	Ref	Ref	Ref
Q2: 1417-3634 MET-min/week	0.99 (0.71-1.38) 0.93	1.00 (0.72-1.41) 0.98	1.04 (0.74-1.46) 0.84
Q3: 3635-7265 MET-min/week	0.87 (0.62-1.22) 0.42	0.89 (0.63-1.26) 0.51	0.90 (0.63-1.28) 0.56
Q4: >7265 MET-min/week	0.44 (0.30-0.65) <0.001	0.53 (0.35-0.78) 0.001	0.54 (0.36-0.81) 0.003
P for linear trend	<0.001	0.001	0.002
White matter hyperintensities, Fazekas scale ≥2			
Regular exercise (yes/no)	0.67 (0.54-0.82) <0.001	0.76 (0.61-0.95) 0.02	0.78 (0.62-0.99) 0.04
Physical activity (per 1000 MET-min/week)	0.97 (0.95-0.99) <0.001	1.01 (0.99-1.03) 0.39	1.01 (0.99-1.03) 0.45
Q1: <1417 MET-min/week	Ref	Ref	Ref
Q2: 1417-3634 MET-min/week	0.95 (0.71-1.26) 0.71	1.04 (0.76-1.43) 0.81	1.06 (0.77-1.46) 0.73
Q3: 3635-7265 MET-min/week	0.82 (0.61-1.09) 0.17	0.90 (0.66-1.24) 0.53	0.90 (0.65-1.25) 0.53
Q4: >7265 MET-min/week	0.72 (0.54-0.96) 0.03	1.16 (0.84-1.60) 0.38	1.16 (0.84-1.62) 0.37
P for linear trend	0.01	0.57	0.58

Physical activity: MET-minutes per week were calculated from the international physical activity questionnaire (IPAQ) and age-adapted according to the American College of Sports medicine[22]

Model 1: univariable, Model 2: adjusted for age and sex, Model 3: additionally adjusted for smoking status, atrial fibrillation type (paroxysmal vs non paroxysmal), hypertension, diabetes mellitus, heart failure, coronary heart disease, statin therapy, antihypertensive medication, oral anticoagulation, antiplatelet therapy

Missing values: Cerebral microbleeds (n=46), white matter hyperintensities (n=1), heart failure (n=1); CI = Confidence interval; MET = metabolic equivalent of task; OR = odds ratio; Q = quartile.

Table 4: Association of regular exercise and weekly physical activity with total brain volume and cognitive function

All patients (n = 1490)	Model 1	Model 2	Model 3
	β (95% CI), p-value	β (95% CI), p-value	β (95% CI), p-value
Normalized brain volume (ml)			
Regular exercise (yes/no)	23.43 (13.81-33.04) <0.001	14.43 (6.05-22.80) <0.001	10.73 (2.37-19.09) 0.01
Physical activity (per 1000 MET-min/week)	3.41 (2.58-4.25) <0.001	1.39 (0.63-2.15) <0.001	1.40 (0.65-2.15) <0.001
Q1: <1417 MET-min/week	Ref	Ref	Ref
Q2: 1417-3634 MET-min/week	26.50 (13.06-39.95) <0.001	24.45 (12.69-36.20) <0.001	21.76 (10.18-33.34) <0.001
Q3: 3635-7265 MET-min/week	26.49 (13.02-39.96) <0.001	21.46 (9.69-33.23) <0.001	18.69 (7.08-30.31) 0.002
Q4: >7265 MET-min/week	51.48 (38.04-64.91) <0.001	28.47 (16.53-40.40) <0.001	25.75 (13.96-37.54) <0.001
P for linear trend	<0.001	<0.001	<0.001
Cognitive Construct (CoCo)			
Regular exercise (yes/no)	0.10 (0.05-0.14) <0.001	0.09 (0.04-0.13) <0.001	0.08 (0.03-0.12) <0.001
Physical activity (per 1000 MET-min/week)	-0.004 (-0.01-0.00) 0.08	-0.004 (-0.01-0.00) 0.07	-0.004 (-0.01-0.00) 0.06
Q1: <1417 MET-min/week	Ref	Ref	Ref
Q2: 1417-3634 MET-min/week	0.03 (-0.03-0.09) 0.30	0.02 (-0.03-0.09) 0.39	0.02 (-0.04-0.08) 0.44
Q3: 3635-7265 MET-min/week	0.04 (-0.02-0.10) 0.18	0.04 (-0.02-0.10) 0.22	0.03 (-0.03-0.09) 0.28
Q4: >7265 MET-min/week	0.001 (-0.06-0.06) 0.98	-0.007 (-0.07-0.05) 0.83	-0.01 (-0.07-0.05) 0.70
P for linear trend	0.90	0.93	0.79

Physical activity: MET-minutes per week were calculated from the international physical activity questionnaire (IPAQ) and age-adapted according to the American College of Sports medicine[22]

Normalized brain volume: Model 1 is univariable, Model 2: adjusted for age and sex, Model 3: additionally adjusted for smoking status, atrial fibrillation type (paroxysmal vs non paroxysmal), hypertension, diabetes mellitus, heart failure, coronary heart disease, statin therapy, antihypertensive medication, oral anticoagulation, antiplatelet therapy.

CoCo: Model 1 is adjusted for age, sex and education; Model 2: additionally adjusted for smoking status, atrial fibrillation type (paroxysmal vs non paroxysmal), hypertension, diabetes mellitus, heart failure, coronary heart disease, statin therapy, antihypertensive medication, oral anticoagulation, antiplatelet therapy; Model 3: additionally adjusted for presence of ischemic infarct or moderate to severe white matter disease on bMRI

Missing values: white matter hyperintensities (n=1), heart failure (n=1); CI = confidence interval; CoCo = cognitive construct; MET = metabolic equivalent of task; bMRI = brain magnetic resonance imaging; Q = quartile.

Figure 1: Prevalence (%) of vascular brain lesions stratified by regular exercise

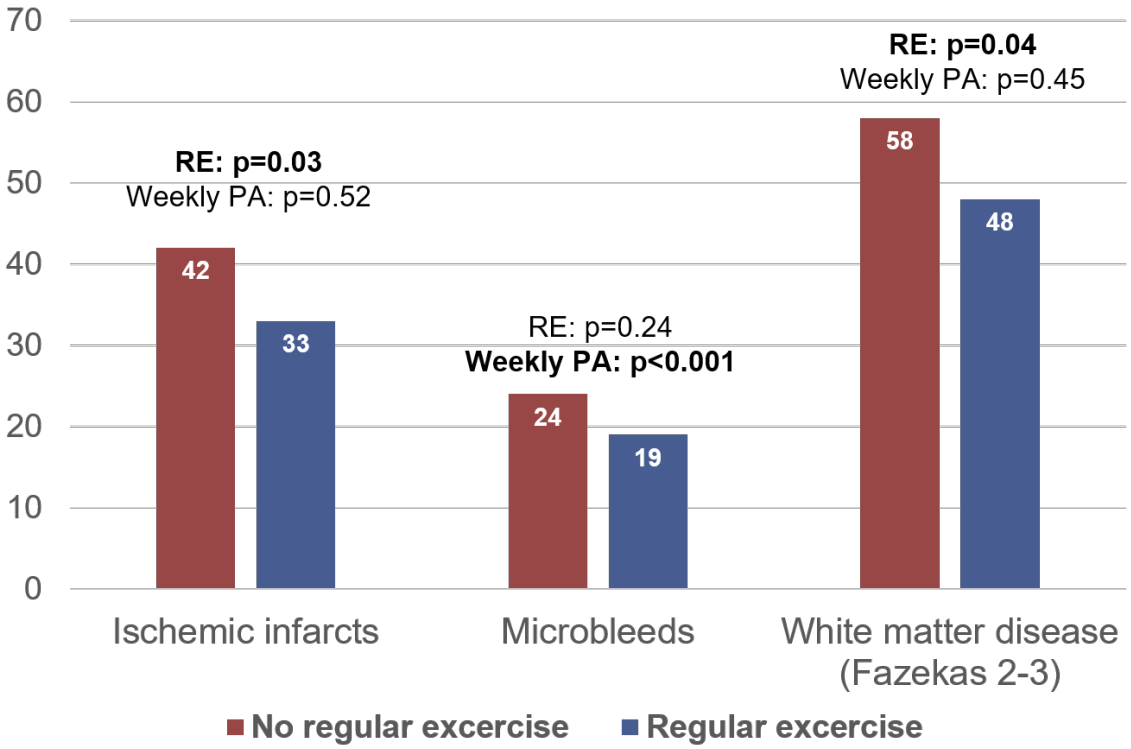
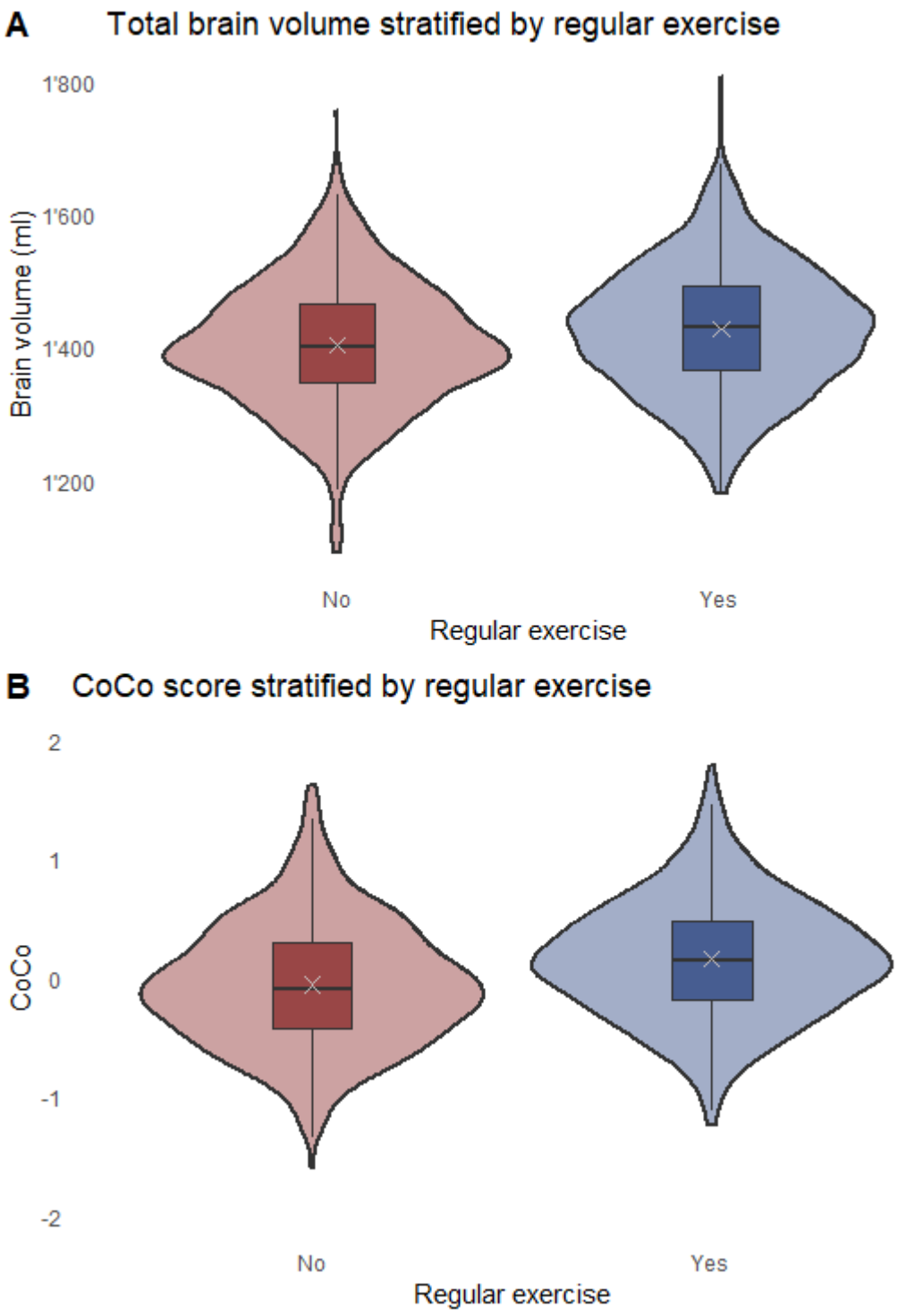


Figure 2: Total brain volume (ml) and cognitive construct (CoCo) score stratified by regular exercise



MANAGE-PD

Tool for Making Informed Decisions to **Aid Timely Management of Parkinson's Disease**

MANAGE-PD allows you to:

- Identify PD patients inadequately controlled on oral medications
- Determine which patients with PD may be adequately controlled on their current treatment regimen or may require changes to their treatment regimen

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PD: Parkinson´s Disease

Parkinson's Foundation

Veeva Code: ABBV-AA-00335-FM Approved: January 2022

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