

# Association of Cardiorespiratory Fitness and Morphological Brain Changes in the Elderly: Results of the Austrian Stroke Prevention Study

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## Key Words

Physical activity · Cardiorespiratory fitness · Cerebral small-vessel disease · White matter lesions · Exercise ECG

## Abstract

**Background:** Physical activity and cardiorespiratory fitness relate to better cognitive performance. Little is known about the effects of fitness on structural brain abnormalities in the elderly. **Objective:** Assess the association between maximal oxygen consumption (VO<sub>2</sub>max), white matter lesion (WML) volume and brain parenchymal fraction (BPF) in a large cohort of community-dwelling elderly individuals. **Methods:** The study population consisted of 715 participants of the Austrian Stroke Prevention Study who underwent brain MRI with semi-automated measurement of WML volume (cm<sup>3</sup>) and automated assessment of BPF (%) by the use of SIENAX. A maximal exercise stress test was done on a bicycle ergometer. VO<sub>2</sub>max was calculated based on maximum and resting heart rate. **Results:** After adjustment for possible confounders, VO<sub>2</sub>max was independently associated with WML volume ( $\beta = -0.10$ ;  $p = 0.02$ ); no significant relationship existed with silent cerebral infarcts and BPF. Associations between VO<sub>2</sub>max and WML load were only significant in men, but not in women. **Conclusion:** Our findings may have important

preventive implications because WMLs are known to be a major determinant of cognitive decline and disability in old age.

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## Introduction

Numerous studies reported a positive relationship between physical activity and cognitive functioning in the elderly [1]. Objectively determined cardiorespiratory fitness (CRF) is closely related to self-reported physical activity assessment, but it is a stronger predictor of health outcomes including cognition [2]. The mechanism(s) behind this association are widely unknown. Neuroimaging data suggest that higher CRF relates to decreased loss of brain tissue with aging [3], but previous investigations did not study the full spectrum of age-related brain abnormalities that might be prevented. Thus, we performed ergometer testing and brain MRI in a community-dwelling cohort of 715 individuals and explored the cross-sectional relationship between maximum oxygen consumption (VO<sub>2</sub>max) and ischemic cerebral damage as well as brain parenchymal fraction (BPF) which represents a measure of brain atrophy. We speculated lower VO<sub>2</sub>max

**Table 1.** Relationship between VO<sub>2</sub>max and WML load and BPF: linear regression analysis

	Total sample			Men			Women		
	β	p	95% CI	β	p	95% CI	β	p	95% CI
<b>Model 1</b>									
WML load <sup>a</sup> , log transformed	-0.10	0.006	-0.34 to 0.06	-0.13	0.006	-0.49 to -0.08	-0.04	0.351	-0.30 to 0.11
BPF <sup>a</sup> , %	0.002	0.728	-0.01 to 0.01	0.003	0.656	-0.01 to 0.01	0.002	0.726	-0.01 to 0.01
<b>Model 2</b>									
WML load <sup>b</sup> , log transformed	-0.10	0.021	-0.36 to 0.03	-0.13	0.012	-0.50 to -0.06	-0.03	0.609	-0.31 to 0.18
BPF <sup>b</sup> , %	0.002	0.829	-0.01 to 0.01	0.003	0.619	-0.01 to 0.01	-0.001	0.909	-0.01 to 0.01

<sup>a</sup> Model 1: adjusted for age and sex.

<sup>b</sup> Model 2: model 1 plus adjustment for hypertension, BMI, cholesterol, smoking status, diabetes and treatment with β-blockers or calcium channel blockers.

to be associated with higher frequency of brain infarction, greater volume of white matter lesions (WMLs) and more brain atrophy.

## Methods

The Austrian Stroke Prevention Study is a prospective community-based cohort study in elderly subjects without dementia and previous strokes [4]. In the present study, we included all 715 individuals who underwent cycle exercise ECG and brain MRI at the same panel of examination and reported no clinical or ECG evidence for myocardial infarction and atrial fibrillation. The mean age of the present sample was 65 ± 8 years (range 44–83) and 54% were women. Risk factors were determined as previously described [4]. There were 67% hypertensives, 8% diabetics and 12% current smokers. The BMI and cholesterol levels were 26.7 ± 3.8 and 225.8 ± 39.8 mg/dl. A total of 12 and 9% of participants were on β-blockers and calcium channel blockers, respectively. All subjects underwent a graded exercise stress test on a cycle ergometer in which exercise intensity was progressively increased by 25 W at 2-min intervals until exhaustion or achievement of the maximum estimated heart rate. VO<sub>2</sub>max was calculated by the equation 15 × body weight (kg) × maximum heart rate/resting heart rate.

Brain MRI scans were obtained on a 1.5-tesla scanner. For WML volume measurement, two experienced investigators marked and outlined each WML on a transparency which was overlaid on the proton density scans, and lesion load measurements were done as described elsewhere [4]. WML load was measured in all 715 participants. Silent cerebral infarct included both lacunes and thromboembolic infarcts. Electronic MRI data for assessment of BPF were available in 537 individuals. BPF was calculated from the T<sub>2</sub>-weighted spin echo sequence using the fully automated structural image evaluation of atrophy (SIENAX, part of FMRIB's Software Library, FSL: <http://www.fmrib.ox.ac.uk/fsl>). Statistical analysis was done by SPSS Statistics 17.0. Linear regression and logistic regression analyses were performed to es-

timate the association between VO<sub>2</sub>max, WML load, BPF and silent cerebral infarct. WML load was positively skewed and thus log-transformed. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity and homoscedasticity by inspecting the normal probability plot of the regression standardized residuals and the scatter plot of the standardized residuals. Two models were assessed. Model 1 was adjusted for age and sex. Model 2 included model 1 covariates plus other factors known to influence either VO<sub>2</sub>max or any of the outcome variables. These additional covariates were hypertension, diabetes, smoking status, total cholesterol, BMI and treatment by β- and calcium channel blockers.

## Results

The VO<sub>2</sub>max of study participants ranged from 0.7 to 3.9 l/min (mean 2 ± 0.4). WML load ranged from 0 to 78 cm<sup>3</sup> with a median of 0.8 cm<sup>3</sup> (interquartile range 0.2–2.8). There were 43 (6.1%) subjects with silent cerebral infarct. BPF ranged from 66 to 87% with a mean of 80 ± 4.0. The associations between VO<sub>2</sub>max and brain MRI findings are displayed in table 1. As shown in table 1, VO<sub>2</sub>max was significantly related to WML load but not to BPF (model 1). The association with WML load remained significant after adjustment for risk factors and treatment with β- and calcium channels blockers (model 2). When adding each single risk factor to model 1, there was no significant change in the effect size of VO<sub>2</sub>max on WML load. Furthermore, the association between VO<sub>2</sub>max and WML load was only significant in men, but not in women. The p values we report in table 1 are not corrected for multiple comparisons. No significant relationship was observed between VO<sub>2</sub>max and silent cerebral infarct.

## Discussion

Our study provides evidence of a protective effect of CRF on WML load. This effect was only significant in men. We failed to confirm a significant relationship between CRF and brain atrophy [3, 5]. There are several explanations for the observed associations. Firstly, higher VO<sub>2</sub>max may be related to better oxygen supply of the brain and thus may protect against the development of WMLs which presumably result from incomplete cerebral ischemia [4]. Secondly, it is possible that the protective effect of CRF on WML volume relates to lower frequencies of vascular risk factors in people with higher fitness levels. This explanation is not corroborated by the results of the present study in which the effect of VO<sub>2</sub>max on WML volume was not mediated by risk factors. Thirdly, regular physical exercise might influence cerebral expression of yet undetermined factors that are involved in WML development or repair. One of many possible candidates is the brain-derived neurotrophic factor (BDNF) which protects against cerebral ischemia [6]. Genetic association studies indicated that BDNF polymorphisms are associated with greater volumes of WML in elderly subjects, and it was also reported that BDNF gene variants exert sex-specific differential effects [7, 8]. We will now measure BDNF plasma concentrations in our study participants to further explore the role of this factor in the association between fitness level and cerebral WML load. However, due to the cross-sectional design of the present study, it is possible that the association between CRF and WML is explained by the more sedentary lifestyle of those with WMLs. The lack of association between CRF and silent cerebral infarct is most probably due to low statistical power associated with small sample size. We can only speculate on the reasons for the observed lack of associa-

tion between CRF and brain atrophy in our study. This result contrasts all previous investigations [3, 5]. However, we measured BPF while previous investigations studied regional brain atrophy which is a more specific marker for ongoing neurodegenerative disease. The lack of regional atrophy measurements, the cross-sectional study design and the indirect determination of VO<sub>2</sub>max from heart rate measurements are limitations of the present investigation. We performed multiple tests by investigating 2 primary phenotypes, WML and BPF and by using 2 statistical models in the regression analyses, in model 1 adjusting for age and sex and in model 2 for additional possible confounders to see if the effect size was changed. Finally, we also explored the association in males and females. Although due to multiple tests the possibility of false-positive findings is enhanced, it should be noted that the tests are not independent and that the proportion of statistically significant findings is much higher than 5% which one would expect by chance. The strengths of the present study include the large number of community-dwelling individuals studied and the extensive diagnostic workup including brain MRI. In conclusion, this is the first study demonstrating protective effects of CRF on WML volume. Given the multiple clinical consequences of WMLs including cognitive decline, gait disturbances, urinary incontinence and mood changes, these findings are likely to have preventive implications. Further investigation of the relationship between cardiorespiratory fitness and cognition in our cohort is under way.

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