Fitness and cognition in the elderly

The Austrian Stroke Prevention Study

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ABSTRACT

Objective: To investigate whether greater cardiorespiratory fitness is associated with better global and domain-specific cognitive function.

Methods: We investigated 877 participants (aged 65 ± 7 years, 55% women) of the Austrian Stroke Prevention Study. For cardiorespiratory fitness, the maximum oxygen consumption ($\dot{V}O_2$max) was calculated based on weight and maximum and resting heart rate on a treadmill test ($mL \cdot kg^{-1} \cdot min^{-1}$). A test battery assessing memory (Bäumler's Lern-und Gedächtnistest), executive function (Wisconsin Card Sorting Test, Trail Making Test–Part B, Digit Span Backward, Alters Konzentrationstest, a computerized complex reaction time task) and motor skills (Purdue Pegboard Test) was administered. Summary measures for cognitive domains and for global cognition were calculated. White matter lesions, lacunes, and brain atrophy were assessed using MRI.

Results: Higher $\dot{V}O_2$max was associated with better global (B = 0.024; $p = 0.000$) and domain-specific cognitive function (memory B = 0.026, $p = 0.000$; executive function B = 0.009, $p = 0.003$; motor skills B = 0.012, $p = 0.018$) after adjustment for age, sex, education years, and Ca^{2+} channel antagonists or β-blockers. White matter lesions, lacunes, or brain atrophy did not mediate the effect ($p > 0.05$ for all mediators). The interactions of $\dot{V}O_2$max with age, overweight, and *APOE* ε4 on cognition were not statistically significant ($p > 0.05$ for all interaction terms) with the exception of a modulating effect of body mass index on $\dot{V}O_2$max in the memory domain.

Conclusions: Higher $\dot{V}O_2$max is associated with better global cognitive function and with better performance in the cognitive domains of memory, executive function, and motor skills in the middle-aged and elderly. The association is not mediated by the presence of white matter lesions, lacunes, and brain atrophy. ***Neurology*® 2016;86:418–424**

GLOSSARY

BMI = body mass index; **BPF** = brain parenchymal fraction; **LGT** = Lern-und Gedächtnistest; **TE** = echo time; **TR** = repetition time; **$\dot{V}O_2$max** = maximum oxygen consumption; **WML** = white matter lesion.

Physical activity[1] and cardiorespiratory fitness[2] have been previously associated with cognitive function in the elderly, and the reduction of Alzheimer and Parkinson disease risk.[3] Nevertheless, there is a substantial amount of variability in the results linking cognitive performance to physical activity because of heterogeneity in the assessments across the studies.[4] While physical activity and cardiorespiratory fitness are intertwined, their relationships with cognitive performance may be distinct from another. Cardiorespiratory fitness is frequently assessed as the maximum oxygen consumption ($\dot{V}O_2$max), which progressively declines with age,[5] but can be increased by prolonged exercise even in the elderly.[6] Cross-sectional observational studies in the elderly found a protective effect of $\dot{V}O_2$max on memory[7] and executive function.[8] Similarly, exercise interventional trials improving $\dot{V}O_2$max reported improvements in executive function[9] and short-term memory.[10] The mechanism linking higher $\dot{V}O_2$max to cognition is, however, not well understood. Neuroprotective or -generative effects,[11] improvements in cerebrovascular function,[12] and indirect effects through a healthier lifestyle[13] have been implicated.

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Supplemental data at Neurology.org

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Comprehensive studies investigating the association between $\dot{V}O_2$max and cognition in the elderly are sparse.[14] Therefore, we studied the effect of $\dot{V}O_2$max on both global and domain-specific cognitive function in 877 elderly individuals of the Austrian Stroke Prevention Study who underwent exercise ECG, neuropsychological testing, and brain MRI. We also tested whether the effect of $\dot{V}O_2$max on cognitive functions is mediated by MRI correlates of brain aging, such as white matter lesions (WMLs), brain parenchymal fraction (BPF), and lacunes.

METHODS

Study population. The Austrian Stroke Prevention Study is a community-based cohort study on the effects of vascular risk factors on brain structure and function in elderly participants without a history or signs of stroke and dementia on the inhabitants of Graz, Austria.[15,16] Study characteristics can be found in table 1. The participation rate was 32.4%. Telephone interviews with 200 random nonresponders yielded no significant differences to responders regarding demographics and frequency of vascular risk factors known to the participants.

The current study cohort comprised 877 participants from 2 panels (1991–1994 and 1999–2003). A subset of 762, 782, and 594 participants additionally underwent MRI measures for WML volume, BPF, and lacunes, respectively. *APOE* genotype was available for a subset of 780 participants.

Table 1 Characteristics of participants from the Austrian Stroke Prevention Study who contributed to the current study

Age, y, mean ± SD	65 ± 7.7
Female, n (%)	487 (55)
Mass-specific $\dot{V}O_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$), mean ± SD	26.43 ± 4.60
Years of education, mean ± SD	11 ± 2.6
Smoking status, n (%)	104 (12) former; 256 (29) current
BMI, kg/m^2, mean ± SD	26.6 ± 3.8
Total cholesterol, mg/dL, mean ± SD	226 ± 39
Diabetes mellitus, n (%)	89 (10)
Hypertension or antihypertensive treatment, n (%)	603 (68)
Metabolic syndrome, n (%)	248 (28)
Previous cardiovascular disease, n (%)	336 (38)
APOE ε4 carriers, n (%)	146 (19)
Log WMLs, median ± IQR	0.58 ± 1.19
BPF, median ± IQR	0.797 ± 0.054
Presence of lacunes, n (%)	42 (5)

Abbreviations: BMI = body mass index; BPF = brain parenchymal fraction; IQR = interquartile range; WML = white matter lesion.

Clinical history, blood tests, MRI, cognitive testing, and exercise ECG were done on the same day. Smoking status was coded as current, former, or never, and participants were considered current smokers if they smoked >10 cigarettes a day. Body mass index (BMI) was calculated in kilograms per square meter. Total cholesterol was determined using a commercially available kit (MA-Kit 100; Hoffmann-La Roche, Basel, Switzerland). Hypertension was considered present if repeated blood pressure was ≥160/95 mm Hg or if participants received medication. Diabetes was considered present if fasting blood glucose levels exceeded 140 mg/dL or participants received medication.[15,16] Assessment of metabolic syndrome and cardiovascular disease is described elsewhere.[17,18]

Standard protocol approvals, registrations, and patient consents. We received approval from the local standard ethics committee of the Medical University of Graz for experiments using human participants. Written informed consent was obtained from all study participants.

Exercise protocol. All participants completed a graded exercise stress test on a treadmill ergometer (General Electric Case V6) supervised by a cardiologist. None of the participants who underwent exercise ECG had clinical or ECG evidence for myocardial infarction or atrial fibrillation.

The protocol consisted of progressive increments of 25 W at 2-minute intervals. According to standard guidelines, reasons for breakoff were occurrence of angina pectoris or dyspnea, ECG ST segment changes, malignant arrhythmias, hypertension >240 mm Hg systolic blood pressure, or achievement of maximum heart rate. The stress tests were performed in the morning hours. Heart rate and blood pressure were measured in sitting position at rest and during exercise in 2-minute intervals. ECG was recorded continuously. Mass-specific $\dot{V}O_2$max was calculated by the following formula: $(15\ mL \cdot kg^{-1} \cdot min^{-1}) \times$ maximum/resting heart rate.[19]

Cognitive testing. A test battery assessing the cognitive domains of memory, motor skills, and executive function was administered as described previously[15,16] and references are listed in appendix e-1 on the *Neurology*® Web site at Neurology.org.

To evaluate memory, a test called Bäumler's Lern-und Gedächtnistest (LGT) was used. Motor skills were evaluated by the Purdue Pegboard Test. Executive function was assessed by the Wisconsin Card Sorting Test, Trail Making Test–Part B, and Digit Span Backward, which is part of the Wechsler Adult Intelligence Scale–Revised, the Alters Konzentrationstest, and a computerized complex reaction time task (Wiener Reaktionsgerät), which is part of the Schuhfried psychological test battery.

Summary measures of cognitive functions were calculated by converting test results to z scores and computing the average scores within each cognitive domain. The z scores were not adjusted for age, sex, and education.

We additionally calculated a measure of global cognitive ability from all cognitive domains.[20]

The listwise n was 765 and the Pearson correlation factor among the 7 tests ranged from 0.130 to 0.531, with a mean of 0.331. Principal components analysis was applied to the 7 tests. The first unrotated principal component accounted for 42.9% of the total test variance and was used as the global cognition in our subsequent analyses. Loadings on the first unrotated principal component were as follows: Alters Konzentrationstest, 1 = −0.538; figural memory (LGT), 2 = 0.646; verbal memory (LGT), 3 = 0.730; complex reaction time task, 4 = −0.541; Digit Span Backward, 5 = 0.594; Purdue Pegboard Test, 6 = 0.723; and Trail Making Test–Part B, 7 = −0.771.

MRI. All MRI scans were performed on 1.5T supraconducting magnets (Gyroscan S 15 and ACS; Philips, Eindhoven, the Netherlands) using proton density- and T2-weighted sequences (repetition time [TR]/echo time [TE] = 2,000–2,500 milliseconds [ms]/30–90 ms) in the transverse orientation and T1-weighted images (TR/TE = 600/30 ms) in the sagittal plane. The slice thickness was 5 mm and the matrix size was 128 × 256 pixels. An axial fluid-attenuated inversion recovery sequence (TR = 10,000 ms, TE = 69 ms, inversion time = 2,500 ms, number of slices = 40, slice thickness = 3 mm, in-plane resolution = 0.86 × 0.86 mm) was added to the initial magnetic resonance protocol in the second study phase between 1999 and 2003. Assessment of brain abnormalities was only done on the dual-echo T2-weighted but not on fluid-attenuated inversion recovery scans to rely on identical MRI sequences throughout the study.

For WML volume measurements, the scans were analyzed by 2 experienced investigators who were blinded to clinical data of study participants. WMLs were graded according to our scheme. All punctate early confluent and confluent WMLs in the deep and subcortical white matter and periventricular WMLs irregularly extending into the deep white matter were marked and outlined on a transparency that was overlaid on the proton density scan. Periventricular caps, pencil-thin lining, and periventricular halos were not included for WML volume measurement as these changes are considered to be of nonischemic origin.

Independent from visual analysis, lesion load measurements were done on proton density–weighted images on an UltraSPARC workstation (Sun Microsystems, Santa Clara, CA) by a trained operator using DISPImage. The operators used a hardcopy overlaid by the transparency, with each single lesion outlined by the experienced readers as reference. Every single lesion was segmented on the computer image, and its area was provided by the semiautomated thresholding algorithm implemented in DISPImage. Each lesion volume was calculated by multiplying the area by slice thickness. Total WML volume in cubic millimeters was the sum of volumes of single lesions in a given study participant.

Lacunes were defined as focal lesions that involved the basal ganglia, internal capsule, thalamus, or brainstem, not exceeding a diameter of 15 mm.

Brain volume was calculated from the T2-weighted spin-echo sequence using the automated structural image evaluation of atrophy (SIENAX, part of the FMRIB Software Library; http://www.fmrib.ox.ac.uk/fsl). BPF was estimated from the ratio of parenchymal volume to the total volume given by the outer surface of the brain.

To determine the measurement errors in our dataset, 20 participants were scanned and rescanned after shortly leaving the scanner. The median relative error for SIENAX was 1.2%.

Statistical analysis. Only cases with no missing data were included in the analyses. Normal distributions were tested with the Kolmogorov-Smirnov test and evaluation of quantile-quantile plots. WML volume had a skewed distribution containing zero values and therefore the value 1 was added before natural log transformation.

We assessed the relationship between $\dot{V}O_2$max and cognition in 2 linear regression models. Model 1 was adjusted for age, sex, years of education, and treatment with Ca^{2+} channel antagonists or β-blockers. Model 2 additionally incorporated vascular risk factors, namely, hypertension, diabetes, total cholesterol, smoking status, and BMI. Sources of potential bias include the indirect assessment of $\dot{V}O_2$max and residual confounding through unaccounted lifestyle variables.

To assess the association between $\dot{V}O_2$max and WMLs, lacunes, and BPF, linear regression models including the same set of covariates, except for years of education, were performed. Multicollinearity was assessed between the independent variable $\dot{V}O_2$max and the confounders in the models using the variance inflation factor. The mean variance inflation factor was 1.250 with values ranging from 1.052 to 1.938, therefore no covariates had to be excluded from the models. For each regression coefficient, the 95% confidence interval and p value were determined. A 2-tailed p value <0.05 was considered to be statistically significant.

To test the hypothesis that $\dot{V}O_2$max effects on cognition are mediated by MRI findings, we used simple bootstrapped mediation models for estimating indirect effect sizes using PROCESS.[21] Mediation was assessed for each of the MRI measures individually.

In addition, stratified analysis was performed using the median for age, binary carrier status for *APOE* ε4, as well as 3 groups for BMI (≤25, 26–29, and ≥30 kg/m^2). Interaction terms of age, *APOE* ε4, and BMI were calculated by multiplying the variables individually with $\dot{V}O_2$max and added to model 2 of the regression to investigate interaction effects.

To determine possible dose-effect relationships of significant associations between $\dot{V}O_2$max and cognitive outcomes, participants were categorized into $\dot{V}O_2$max quartiles. Linear regression analyses with $\dot{V}O_2$max quartiles and cognitive measures adjusted for confounders similar to model 2 were performed, in which the lowest quartile of $\dot{V}O_2$max values served as the reference. A p value for the trend was calculated by including the quartiles as a continuous variable in the model.

Because of the explorative nature of the study, no corrections for multiple testing were made.[22]

RESULTS Higher $\dot{V}O_2$max was associated with better global and domain-specific cognition after adjustment for age, sex, and education, and Ca^{2+} and β-blocker use (table 2). Addition of vascular risk factors in model 2 had no effect on our observations, with the exception of motor skills, which was no longer associated.

Subsequently, we investigated whether the effect of $\dot{V}O_2$max on cognition was mediated by the presence of lacunes, WML volume, and BPF (table 3), but found no evidence for this assumption. As we previously reported, absolute $\dot{V}O_2$max was associated with volume of WMLs in our cohort, but not with lacunes or BPF (table e-1).[23]

Next, we assessed whether the association between $\dot{V}O_2$max and cognition was restricted to subgroups, by stratifying for age, BMI, and *APOE* ε4 carrier status, which revealed a confined effect in younger participants (aged ≤65 years), participants with lower BMI (≤25 kg/m^2), and in *APOE* ε4 noncarriers (table 4).

Formal test for interactions for memory, executive function, and global cognition were not significant for either age (B = −0.01, p = 0.084; B = 0.000, p = 0.254; B = 0.000, p = 0.999) or *APOE* ε4 carrier status (B = 0.000, p = 0.883; B = −0.002, p = 0.105; B = −0.002, p = 0.370).

Table 2 Linear regression analyses of the association of $\dot{V}O_2$max with cognitive measures

	Model 1		Model 2	
	B (95% CI)	*p* Value	B (95% CI)	*p* Value
Memory	0.026 (0.013–0.038)	0.000	0.025 (0.012–0.038)	0.000
Executive function	0.009 (0.003–0.015)	0.003	0.009 (0.003–0.016)	0.003
Motor skills	0.012 (0.002–0.022)	0.018	0.009 (−0.001–0.020)	0.078
Global cognition	0.024 (0.012–0.035)	0.000	0.022 (0.011–0.034)	0.000

Abbreviation: CI = confidence interval.
Dependent variables: memory, executive function, motor skills, and global cognition; predictor variable: mass-specific $\dot{V}O_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$). Effect size B is given as change in *z* score in the cognitive domains by 1 $mL \cdot kg^{-1} \cdot min^{-1}$ change in $\dot{V}O_2$max. Model 1 is adjusted for age, sex, years of education, and Ca^{2+} and β-blocker use. Model 2 is adjusted for age, sex, years of education, Ca^{2+} and β-blocker use, smoking status, body mass index, total cholesterol, hypertension, and diabetes.

We observed an interaction between $\dot{V}O_2$max and BMI on memory, but not executive function or global cognition (B = −0.003, $p = 0.043$; B = −0.001, $p = 0.450$; B = −0.001, $p = 0.412$).

We further explored the association between $\dot{V}O_2$max and cognition by analyzing the effect of quartiles of the $\dot{V}O_2$max distribution (figure) and discovered a linear trend with memory, executive function, as well as global cognition.

The differences in effect sizes between the lowest and the highest quartile of $\dot{V}O_2$max were 0.298 for memory, 0.117 for executive function, and 0.260 for global cognition. Given that 1 year of age changes the *z* score by −0.045 for memory, by −0.018 for executive function, and by −0.066 for global cognition, individuals in the highest quartile of $\dot{V}O_2$max obtained memory, executive function, and global cognition results typical for participants being 6, 7, and 4 years younger than those belonging to the lowest $\dot{V}O_2$max quartile.

Table 3 Mediation analysis

	Total effect	Direct effect	Indirect effect	Bootstrapped CI
WML volume (n = 762)				
Memory	0.022	0.022	0.000	0.008 to 0.037
Executive function	0.010	0.009	0.000	0.003 to 0.016
Motor skills	0.008	0.008	0.000	−0.002 to 0.019
Global cognition	0.021	0.020	0.001	0.008 to 0.033
No. of lacunes (n = 782)				
Memory	0.025	0.025	0.000	0.011 to 0.038
Executive function	0.010	0.010	0.000	0.003 to 0.017
Motor skills	0.008	0.008	0.000	−0.003 to 0.018
Global cognition	0.022	0.021	0.000	0.009 to 0.034
BPF (n = 594)				
Memory	0.025	0.025	0.000	0.009 to 0.040
Executive function	0.007	0.007	0.000	0.000 to 0.014
Motor skills	0.008	0.008	0.000	−0.005 to 0.020
Global cognition	0.019	0.019	0.000	0.004 to 0.033

Abbreviations: BPF = brain parenchymal fraction; CI = confidence interval.
Dependent variable: memory, executive function, motor skills, and global cognition; predictor: mass-specific $\dot{V}O_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$) mediators are white matter lesion volume, number of lacunes, and BPF. The model is adjusted for age, sex, years of education, Ca^{2+} and β-blocker use, smoking status, body mass index, total cholesterol, hypertension, and diabetes (model 2).

DISCUSSION In the present study, higher $\dot{V}O_2$max was associated with better global cognition, as well as with better performance in memory, executive function, and motor skills.

The differences in cognitive performance between participants in the highest vs lowest quartile of $\dot{V}O_2$max corresponded to an age difference of 4, 6, and 7 years for global cognition, memory, and executive function. Given that the incidence of Alzheimer disease is increasing exponentially from about 0.5% in the age group of 65–70 years to approximately 6%–8% for individuals older than 85 years by doubling every 5 years, these effect sizes can be considered as large and potentially relevant for preventing or delaying dementia.[24]

The effect of fitness both on global cognition as well as on the specific cognitive domains suggests that better fitness may slow down the process of brain aging in general. In line with this hypothesis, a recent review summarizing the association between physical activity, cardiorespiratory fitness, and dementia concludes that the brain indeed preserves its plasticity to respond to physical activity into late adulthood and that even modest physical activity can reduce the risk of dementia.[25]

Clearly, well-controlled and long-term randomized interventional trials measuring incidence of dementia are needed to formally test this hypothesis.

The widespread effect of $\dot{V}O_2$max on cognition lets us hypothesize that both cortical and subcortical structures are protected by higher $\dot{V}O_2$max. However, we found no mediation of the association by brain atrophy, WMLs, or lacunes in our cohort to support this hypothesis.

Nevertheless, we cannot rule out that microstructural changes, undetectable by conventional MRI, are acting as mediators. Indeed, cross-sectional studies showed an association between microstructural integrity of both normal and hyperintense white matter with cognitive function, regardless of WML volume or brain atrophy,[26] and also reported higher integrity of white matter in physically active individuals.[27]

A 12-month aerobic exercise intervention program observed changes in white matter integrity concomitant with improvement in short-term memory.[10]

Table 4 Association of $\dot{V}O_2$max with cognitive measures stratified for age, *APOE* genotype, and BMI

	Memory		Executive function		Motor skills		Global cognition	
	B (95% CI)	*p* Value	B (95% CI)	*p* Value	B (95% CI)	*p* Value	B (95% CI)	*p* Value
Age, y								
≤65 (n = 443)	0.035 (0.014 to 0.055)	0.001	0.014 (0.005 to 0.023)	0.002	0.019 (0.004 to 0.034)	0.013	0.028 (0.012 to 0.044)	0.001
>65 (n = 409)	0.016 (−0.000 to 0.032)	0.054	0.005 (−0.004 to 0.014)	0.306	−0.001 (−0.016 to 0.013)	0.856	0.017 (0.000 to 0.034)	0.055
***APOE* ε4**								
Noncarrier (n = 634)	0.031 (0.017 to 0.046)	0.000	0.009 (0.002 to 0.017)	0.010	0.010 (−0.002 to 0.022)	0.087	0.023 (0.010 to 0.037)	0.001
Carrier (n = 146)	0.010 (−0.025 to 0.044)	0.582	0.006 (−0.010 to 0.023)	0.458	0.007 (−0.020 to 0.034)	0.620	0.017 (−0.013 to 0.047)	0.273
BMI, kg/m²								
≤25 (n = 322)	0.030 (0.009 to 0.051)	0.005	0.011 (0.000 to 0.021)	0.042	0.008 (−0.008 to 0.024)	0.319	0.023 (0.004 to 0.042)	0.018
26–29 (n = 377)	0.021 (0.002 to 0.040)	0.032	0.012 (0.002 to 0.021)	0.019	0.014 (−0.001 to 0.030)	0.070	0.025 (0.008 to 0.042)	0.004
≥30 (n = 153)	0.025 (−0.009 to 0.060)	0.152	−0.001 (−0.016 to 0.015)	0.925	−0.007 (−0.036 to 0.021)	0.610	0.012 (−0.021 to 0.045)	0.469

Abbreviations: BMI = body mass index; CI = confidence interval.
Dependent variables: memory, executive function, motor skills, and global cognition; predictor variable: mass-specific $\dot{V}O_2$max (mL·kg^{-1}·min^{-1}). Effect size B is given as change in *z* score in the cognitive domains by 1 mL·kg^{-1}·min^{-1} change in $\dot{V}O_2$max. The model is adjusted for age, sex, years of education, Ca^{2+} and β-blocker use, smoking status, BMI, total cholesterol, hypertension, and diabetes.

Figure Quartile analysis distribution of mass-specific $\dot{V}O_2$max, using quartile 1 as reference

The x-axis depicts *z* scores of the respective cognitive outcome. The analysis is adjusted for age, sex, years of education, Ca^{2+} and β-blocker use, smoking status, body mass index, total cholesterol, hypertension, and diabetes.

By stratifying on strong risk factors for dementia, we found that the associations between $\dot{V}O_2$max and cognitive functions were restricted to the middle-aged (younger than 65 years), to *APOE* ε4 noncarriers, and to nonobese individuals. Upon formal testing, we only found an interaction between $\dot{V}O_2$max and BMI in the memory domain. Therefore, we can conclude that the effect of $\dot{V}O_2$max on cognitive outcomes is not modulated by age or *APOE* ε4 carrier status. BMI, however, showed a modulating effect on the association between $\dot{V}O_2$max and memory ($p = 0.043$).

Previous studies reported contradictory findings on the modulating effect of strong risk factors. A meta-analysis of intervention trials concluded that older participants (>65 years) benefit more than younger ones from enhancing their fitness.[28]

While we found no studies investigating *APOE* in a similar setup, a cross-sectional study in the healthy elderly found that poor midlife physical activity is associated with increased risk of developing dementia only in *APOE* ε4 noncarriers.[29]

According to a cross-sectional investigation, the beneficial effect of $\dot{V}O_2$max on cognition and regional brain volume was confined to obese individuals.[30]

The contradictory findings may be partly explained by the relatively small sample sizes, differences in study design, observational vs interventional, and by differences in the characteristics of the individuals investigated.

In the interventional trials, only seniors who were sedentary at baseline were included. Therefore, only a relatively short-term effect of fitness improvements on cognition could be examined compared to observational studies in which a higher average fitness level is likely due to prolonged commitment to regular exercise and/or to beneficial genetic factors. This is

well in line with recent findings of the longitudinal CARDIA study that higher cardiorespiratory fitness in midlife is associated with better performance in psychomotor speed and verbal memory 25 years later.[31]

In the present study, we used $\dot{V}O_2$max as a measure of cardiorespiratory fitness, which represents the maximum capacity of the pulmonary, cardiovascular, and skeletal muscle to uptake, transport, and utilize oxygen during severe exercise.[32] The interindividual variation in $\dot{V}O_2$max is mainly attributable to differences in maximum cardiac output.[32]

$\dot{V}O_2$max itself, as well as its response to exercise, shows a considerable heritability of 25% to 65%.[33] Endurance training can significantly increase $\dot{V}O_2$max, but again large variations between individuals in response to training are present[28]: the improvement of $\dot{V}O_2$max by endurance training is primarily attributable to a higher cardiac output, but increased capillarization and respiratory chain function in the muscle are also discussed.[32] Of note, $\dot{V}O_2$max can be increased by a diversity of training programs even in sedentary elderly participants, which in turn improves cognition, especially executive functions.[34]

The mechanism by which $\dot{V}O_2$max is related to cognitive function is unclear.[35] Exercise is known to enhance cerebral blood flow,[36] capillary density, substrate exchange, and antioxidative mechanisms.[1] Some of the effect of $\dot{V}O_2$max on cognition might also be conveyed indirectly by counteracting depression in the elderly.[37]

Although we found no evidence in the literature, we tentatively hypothesize that $\dot{V}O_2$max may also be indicative of oxygen utilization capacity in the brain as well.

The association between $\dot{V}O_2$max and cognition may be indirect, likely attributable to a more favorable vascular risk factor profile. In fact, high $\dot{V}O_2$max has been associated with reduced risk of cardiovascular disease,[38] insulin resistance,[39] and metabolic syndrome.[40] Our finding that adjustment for vascular risk factors attenuated the association between $\dot{V}O_2$max and motor skills supports this hypothesis.

There are several limitations to our study. The cross-sectional design, which allows measurement of cognition, exercise, and MRI only at a single time point, limits causal inference. Additional insight may be gained by longitudinal studies. Second, $\dot{V}O_2$max was not directly measured using spiroergometry, but calculated from heart rates obtained by exercise ECG. Third, we cannot entirely rule out residual confounding from unavailable lifestyle variables such as diet or physical activity.

Nevertheless, our study has multiple strengths. Above all, we benefit from an extensive phenotypic workup, including an array of cognitive tests and scores for all domains, the availability of MRI, as well as exercise ECG data. Another benefit is the large sample size and the homogeneous community-based elderly cohort.

Further interventional studies are needed to investigate the potential of cardiorespiratory fitness as a therapeutic option against cognitive decline in the elderly. It will be important to identify those individuals who, based on their risk factor profile, will benefit the most from intervention programs.

AUTHOR CONTRIBUTIONS

P. Freudenberger performed the statistical analysis and drafted the manuscript under the supervision of H. Schmidt. K. Petrovic performed the cognitive testing and wrote part of the Methods section. A. Sen contributed to data acquisition of covariates and data analyses. A.M. Töglhofer contributed to data acquisition of covariates and data analyses. A. Fixa contributed to data acquisition of covariates and data analyses. E. Hofer contributed to data acquisition of covariates and data analyses. S. Perl performed the exercise tests and acquisition of $\dot{V}O_2$max and wrote part of the Methods section. R. Zweiker performed the exercise tests and acquisition of $\dot{V}O_2$max and wrote part of the Methods section. S. Seshadri designed the study and drafted the manuscript. R. Schmidt designed the study and drafted the manuscript. H. Schmidt designed the study and drafted the manuscript. All authors proofread the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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