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ORIGINAL ARTICLE

Association Between Exercise Capacity and Late Onset of Dementia, Alzheimer Disease, and Cognitive Impairment

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Abstract

Objective: To address the association between exercise capacity and the onset of dementia, Alzheimer disease, and cognitive impairment.

Patients and Methods: For 6104 consecutive veteran patients (mean ± SD age: 59.2±11.4 years) referred for treadmill exercise testing, the combined end point of dementia, Alzheimer disease, and cognitive impairment was abstracted from the Veterans Affairs computerized patient record system.

Results: After mean ± SD follow-up of 10.3±5.5 years, 353 patients (5.8%) developed the composite end point at a mean ± SD age of 76.7±10.3 years. After correction for confounders in multivariate Cox proportional hazards regression, higher age at exercise testing (hazard ratio [HR]=1.08; 95% CI, 1.07-1.09; $P<.001$), current smoking (HR=1.44; 95% CI, 1.08-1.93; $P=.01$), and exercise capacity (HR=0.92; 95% CI, 0.89-0.96; $P<.001$) emerged as predictors of cognitive impairment. Each 1−metabolic equivalent increase in exercise capacity conferred a nearly 8% reduction in the incidence of cognitive impairment. Meeting the recommendations for daily activity was not associated with a delay in onset of cognitive impairment (HR=1.07; 95% CI, 0.86-1.32; $P=.55$).

Conclusion: Exercise capacity is strongly associated with cognitive function; the inverse association between fitness and cognitive impairment provides an additional impetus for health care providers to promote physical activity.

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In the United States, there is projected to be a considerable increase in the prevalence of individuals 65 years or older in the coming decades, a population that is prone to dementia and its subtle, preclinical forms, collectively termed *cognitive impairment*.[1,2] For this reason, research directed toward the many facets of cognitive function has become an important public health issue. In this context, much attention has been given to the effects of cardiovascular risk factors and cognitive function.[3,4] Multiple observational studies[5-11] have suggested an association between higher systolic blood pressure, dyslipidemia, history of alcohol abuse, smoking, diabetes, and physical inactivity and impairment in cognitive function. These elevated but subclinical cardiovascular risk markers may represent potentially modifiable factors that could delay cognitive decline related to aging. A recent review[12] as well as interventional studies[13-16] suggested that physical activity improves cognitive function by modifying particular cardiovascular and metabolic risk factors. Presently, however, there is insufficient evidence to make clear exercise recommendations for individuals at risk for cognitive decline.[6,8,12]

Physical activity, a major factor in the development of fitness, is an elusive term.[17] Observational studies directed toward cognitive impairment[6,7,18,19] in general derive physical activity from recall questionnaires, which are cost-effective but limited by well-documented inaccuracies, particularly the tendency to overreport activity levels, the inability to accurately capture exercise intensity, and portability.[6,17] Therefore, as a more objective marker in epidemiologic studies, measured exercise capacity is often considered because it is closely related to physical activity levels,[20,21] has demonstrated strong prognostic value for numerous health outcomes,[22,23] and has been found to exceed the prognostic value of physical activity.[20,24]

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The present study, therefore, addressed the question of whether exercise capacity, measured objectively during treadmill exercise testing, was associated with the onset of dementia, Alzheimer disease, or cognitive impairment.

PATIENTS AND METHODS

Study Participants

The study population consisted of 6104 veterans from the Veterans Exercise Testing Study cohort.[23] As described previously,[23,24] the Veterans Exercise Testing Study began in 1987 and is an ongoing, prospective evaluation of veterans referred for exercise testing for clinical reasons that was designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. From these exercise tests, the medical history was abstracted from the Veterans Affairs computerized medical records system.

Historical information was recorded at the time of the exercise test.[24] Smoking was categorized as never, former, or current. Hypercholesterolemia was defined as a cholesterol level greater than 220 mg/dL (to convert to mmol/L, multiply by 0.0259), statin use, or both. Diabetes status was classified as use of insulin or oral hypoglycemic agents. Activity level was quantified by the answer to the following question: "At least 3 times a week, do you engage in some form of regular activity, such as brisk walking, jogging, bicycling, or swimming, long enough to work up a sweat, get your heart thumping, or become short of breath?" Participants who answered "no" to this question were considered as not meeting the minimal criteria for physical activity by the American College of Sports Medicine guidelines[25] and were classified as physically inactive.

Treadmill Exercise Testing

Participants underwent symptom-limited treadmill testing using an individualized ramp treadmill protocol as described previously.[23,24,26] All tests were performed to maximal voluntary exhaustion or to standard criteria for termination, including moderately severe angina, greater than 2.0 mm of horizontal or downsloping ST depression, a sustained decrease in systolic blood pressure, or serious rhythm disturbances. Blood pressure was measured manually, and exercise capacity (in metabolic equivalents [METs]) was estimated from peak treadmill speed and grade.[21] Individuals whose tests were terminated prematurely because of orthopedic or other limitations were excluded.

Outcomes

The primary outcome was a composite of cognitive impairment that included onset of dementia, Alzheimer disease, and early symptoms of cognitive disorder. All diagnoses were established by the treating physician. Relevant *International Classification of Diseases, Ninth Revision* codes included were 290.X (dementia), 331.X (Alzheimer disease), and 294.X (cognitive disorder and cognitive impairment). The outcomes were abstracted from the Veterans Affairs computerized medical records system for all patients as of December 2015. Herein, the term *cognitive impairment* is used for the composite end point.

Data Analyses

All continuous variables are expressed as mean ± SD, and all categorical variables are expressed as numbers and percentages.

Independent predictors of the onset of cognitive impairment were estimated using Cox proportional hazards analysis. Two separate models were developed. First, the effect of exercise variables, anthropometrics, cardiovascular risk factors, and medications were assessed in a univariate model. Second, all variables that exhibited a significant univariate association were tested multivariately. Variables included in the model were age at the time of the test, body mass index (BMI; calculated as calculated as the weight in kilograms divided by the height in meters squared), exercise capacity, history of cardiovascular disease (CVD), hypertension, dyslipidemia, cardiovascular medication use, alcohol abuse, smoking, and diabetes. Kaplan-Meier survival curves were generated to illustrate the association between exercise capacity and onset of cognitive impairment. Receiver operating characteristic curves were used to derive the cutoff value for highest sensitivity and specificity from the multivariate model.

For all the analyses, $P<.05$ was considered statistically significant. All the analyses were

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performed using IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp). The illustration of relative risks for freedom from dementia or cognitive impairment among fitness categories was created using a spreadsheet software program (Microsoft Excel 2013; Microsoft Corp).

RESULTS

Patient characteristics are displayed in Table 1. After mean ± SD follow-up of 10.3±5.5 years, 353 patients (5.8%) developed the combined end point of cognitive impairment at a mean ± SD age of 76.7±10.3 years.

Independent risk factors for cognitive impairment in the univariate model were higher age, lower BMI, lower exercise capacity, history of CVD, current smoker, and use of angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, or statins (Table 2). After correction for confounders in the multivariate model (Table 2), predictors of cognitive impairment were higher age at the time of the exercise test (hazard ratio [HR]=1.08; 95% CI, 1.07-1.09; $P<.001$) and higher exercise capacity (HR=0.92; 95% CI, 0.89-0.96; $P<.001$). Each 1-MET increase in exercise capacity conferred a nearly 8% reduction in the incidence of the composite end point. Smoking increased the risk by 44.1% (HR=1.44; 95% CI, 1.08-1.93; $P=.01$), whereas higher BMI had a slight protective effect (HR=0.97; 95% CI, 0.94-0.99; $P=.002$). Compared with the most fit group (exercise capacity >12 MET), the risk of cognitive impairment was progressively higher as fitness was lower (>9-12 MET: HR=1.84; 95% CI, 1.12-3.04; $P=.02$; 6-9 MET: HR=2.80; 95% CI, 1.74-4.50; $P<.001$; and <6 MET: HR=4.42; 95% CI, 2.77-7.07; $P<.001$) (Figure 1).

Receiver operating characteristic curve analysis revealed that age older than 66.3 years, exercise capacity greater than 8.15 MET, and BMI less than 30.5 had the highest sensitivity and specificity for predicting the onset of dementia and cognitive impairment. Figure 2 illustrates freedom from the composite end point according to the 4 risk factors from the final multivariate model (age, BMI, smoking, and exercise capacity). Meeting the recommendations for daily activity was not associated with a delay in the onset of cognitive impairment in the univariate analysis (HR=1.07; 95% CI, 0.86-1.32; $P=.55$).

TABLE 1. Characteristics of the 6104 Study Participants

Characteristic	Value
Male sex (No. [%])	5888 (96.5)
Age (y), mean ± SD	59.2±11.4
Follow-up (y), mean ± SD	10.3±5.5
BMI	29.0±5.3
Exercise capacity (MET), mean ± SD	8.3±3.4
Risk factors (No. [%])	
History of CVD	1450 (23.8)
History of hypertension	3283 (53.8)
History of dyslipidemia	2318 (40.0)
History of drug use	155 (2.5)
History of alcohol abuse	258 (4.2)
History of diabetes	992 (16.3)
Current smoking	1027 (16.8)
Physically inactive	2710 (44.4)
Medications (No. [%])	
β-Blockers	1369 (22.4)
ACE inhibitors	1469 (24.1)
Antihypertensive agents	991 (16.2)
Diuretics	426 (7.0)
Statins	902 (14.8)

ACE = angiotensin-converting enzyme; BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent.

DISCUSSION

The present results suggest a strong association between objectively determined physical fitness and the development of cognitive impairment. This association holds true even after correction for multiple cardiovascular risk factors.

Physical Fitness and Physical Activity

Exercise stimulates neurogenesis in the hippocampus and enhances gray and white matter volume in the prefrontal and temporal cortical regions, which seems to reflect a type of cognitive reserve.[27-29] Exercise facilitates this process by improving blood flow and oxygen supply to these areas and distributing growth factors and brain-derived neurotrophic factor.[12,28] These factors decrease extracellular amyloid-ß plaques, which are suggested to be the "putative culprit" of Alzheimer disease and other cognitive disorders.[30-32]

Many large cohort studies have previously addressed the potential beneficial effects of

TABLE 2. Univariate and Multivariate Cox Proportional Hazards Analysis for Independent Predictors of Dementia in 6104 Veterans[a]

Predictor	Univariate model			Multivariate model		
	Wald	Hazard ratio (95% CI)	*P* value	Wald	Hazard ratio (95% CI)	*P* value
Age (y)	257.51	1.09 (1.08-1.10)	<.001[b]	149.1	1.08 (1.07-1.09)	<.001[b]
BMI	15.59	0.95 (0.93-0.98)	<.001[b]	9.16	0.97 (0.94-0.99)	.002[b]
Exercise capacity (MET)	84.40	0.84 (0.81-0.87)	<.001[b]	14.19	0.92 (0.89-0.96)	<.001[b]
History of CVD	4.83	1.30 (1.03-1.65)	.03[b]	0.78	0.90 (0.70-1.14)	.38
History of hypertension	3.29	1.22 (0.98-1.45)	.07			
History of dyslipidemia	0.83	1.10 (0.89-1.37)	.36			
History of drug use	0.05	1.10 (0.49-2.47)	.82			
History of alcohol abuse	0.29	1.19 (0.63-2.24)	.59			
History of diabetes	3.45	1.31 (0.99-1.73)	.06			
Current smoker	8.29	1.48 (1.14-1.95)	.004[b]	6.03	1.44 (1.08-1.93)	.01[b]
Physically inactive	0.36	1.07 (0.86-1.32)	.55			
β-Blockers	1.42	1.17 (0.91-1.50)	.23			
ACE inhibitors	5.84	1.36 (1.06-1.75)	.02[b]	0.06	1.04 (0.79-1.36)	.81
Antihypertensive agents	6.05	1.38 (1.07-1.79)	.02[b]	0.01	1.01 (0.77-1.31)	.99
Diuretics	1.83	1.38 (0.86-2.21)	.18			
Statins	7.19	1.55 (1.13-2.14)	.007[b]	1.89	1.27 (0.90-1.80)	.17

[a]ACE = angiotensin-converting enzyme; BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent.
[b]Statistically significant.

physical activity on cognitive function, and these studies suggest a dose-dependent relationship.[6,19,33-35] We did not observe an association between the physical activity criteria used and the end point in univariate analysis.

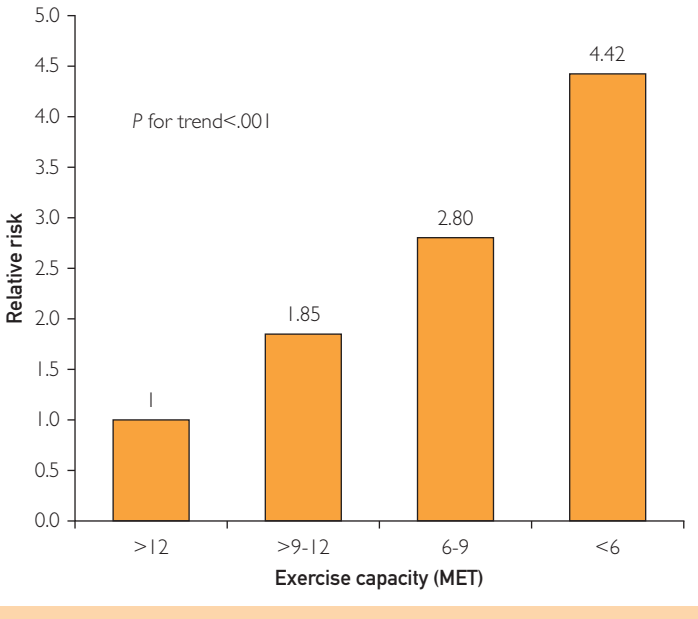

FIGURE 1. Relative risks for freedom from dementia or cognitive impairment among fitness categories, with most fit (exercise capacity >12 metabolic equivalents [MET]) as the reference group.

However, accurate assessment of physical activity, particularly self-assessment, can be fraught with imprecision, as outlined in recent reviews by Hamer and Chida[33] and Kirk-Sanchez and McGough[12] in the context of cognitive decline. Studies using objective measures of fitness from maximal exercise testing are generally small but have characterized an association between peak oxygen uptake (the gold standard measure of physical fitness) and brain plasticity,[36] hippocampal volume,[37] brain atrophy, and tissue density.[29]

The present findings are the first, to our knowledge, to determine that objectively measured physical fitness established by treadmill exercise testing is negatively associated with future onset of cognitive impairment. Moreover, the end point is more precise than that of previous studies because we relied on a diagnosis of dementia, Alzheimer disease, or cognitive impairment established by a clinician and not on a surrogate measure, as was the case in other reports.[6-8,18,38]

Physical fitness was also a more powerful predictor of risk than was physical activity in the present study. Evidence that physical fitness exceeds the prognostic value of physical activity has been suggested in previous reports,[20,24,39] but because few studies have quantified both physical activity patterns and

objectively determined fitness in the same cohort, this issue requires further exploration.[17] In a recent report on all-cause mortality,[24] meeting the physical activity guidelines provided significant net reclassification, but significantly greater risk reclassification was provided by fitness level. Unfortunately, these 2 terms are frequently used interchangeably because they are related to one another. However, one is a behavior (physical activity) and one an attribute (fitness), and, thus, they have different implications physiologically and in terms of outcomes. Given the present and previous results, more attention should be given to the potential associations among physical activity, fitness, and the prevention of cognitive disorders. This is particularly notable given that high-intensity interval training has recently been promoted in cardiac rehabilitation programs.[40,41]

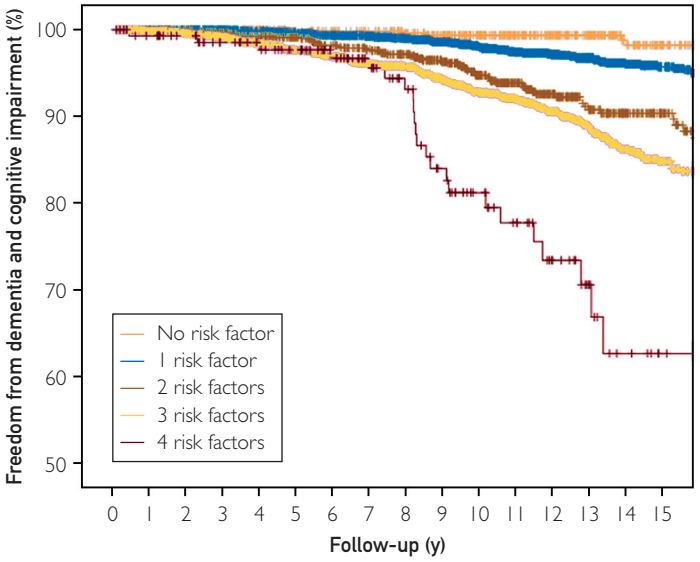

FIGURE 2. Kaplan-Meier curves for freedom from dementia and cognitive impairment clustered for the 4 risk factors at baseline (higher age, lower body mass index, lower exercise capacity, and smoking) from the final multivariate model.

Cardiovascular Risk Factors

Exercise mediates cardiovascular risk factors that are linked to cognitive decline by improving blood pressure, lipid levels, inflammation, glucose tolerance, and endothelial function.[3,12,33] The most critical factor in this context might be hyperinsulinemia. It is known to drive brain amyloid metabolism, which is suggested to be a major underlying factor in Alzheimer disease and other cognitive disorders.[31,32] The findings from the present study are in agreement with previous studies reporting an association between cardiovascular risk factors and various end points related to cognitive functioning.[3-5,8,38] Similar to the study by Arntzen et al,[38] history of CVD as well as smoking showed a significant increase in the probability of developing cognitive impairment. Hypertension and diabetes also tended to worsen the composite outcome in this study. Note that antihypertensive drugs, ACE inhibitors, and statins, widely used for the primary and secondary prevention of CVD, seemed to enhance the probability of cognitive impairment in this cohort. However, the general role of these drugs in the onset of dementia or delay in its progression is not completely understood. Observational studies suggest a beneficial effect of statins,[42] whereas the effect of ACE inhibitors has been debated.[43] Ultimately, it is difficult to distinguish the effect of the drug itself vs an improvement in the cardiovascular risk factor. The present results suggest the latter because there was no effect of these drugs in the multivariate model.

Similar to the findings of the Tromsø Study in men,[38] the effect of the major cardiovascular risk factors in the present study was minimal. In the Tromsø cohort, only smoking persisted as a risk factor for cognitive impairment in each of their 3 cognitive outcomes after adjusting for confounders. In previous studies assessing risk of CVD, smoking was found to have a stronger prognostic value than diabetes and hypertension, particularly in males.[44]

In general, it must be assumed that the effect of age and exercise capacity in the multivariate model exceeded the effect of the other cardiovascular risk factors; undoubtedly, the probability of diabetes, hypertension, history of CVD, and medication use is higher in those with advanced age. Nevertheless, because exercise capacity remained an independent predictor of risk in the multivariate model, it suggests that those with higher physical fitness may engage in exercise to a greater extent and, therefore, have not only a higher exercise capacity but also a more favorable cardiovascular risk profile.

The Role of BMI

The observation that higher BMI was associated with lower incidence of cognitive impairment is surprising on the surface but is in agreement with previous studies in different ethnic groups.[45] However, the literature is controversial regarding midlife or late-life adiposity and its influence on cognition. Although this issue requires further exploration, the possibility that higher weight may be favorably related to cognition suggests a form of an obesity paradox as is currently observed for cardiovascular mortality.[46,47]

In general, overweight and obese individuals are at higher risk for cognitive impairment because adiposity worsens almost all modifiable cardiovascular risk factors that are linked to various metrics of cognitive burden.[3,12,38,48,49] It has been suggested that the relation between BMI and cognitive function does not sufficiently reflect body composition and body metabolism, particularly in elderly populations, which may partially explain the U-shaped curve between BMI and cognitive impairment.[45] It has, therefore, been proposed that hyperinsulinemia, glucose intolerance, diabetes, and other factors, such as hypertension, dyslipidemia, and inflammation, be considered as causal pathways and not just as confounders.[31] Although this research is beyond the scope of the present study, considering the ongoing obesity epidemic in the United States, particularly in children, it underscores calls for action by professional groups to reduce the burden of obesity.[50]

Limitations

Cognitive morbidity before exercise testing could not be entirely ruled out because it was not part of the screening procedure. However, most of the cases of dementia and cognitive impairment developed long after baseline testing (Figure 2), suggesting no reverse causality. This study sample consisted almost entirely of men, and the results may not be applicable to women. Several risk factors, including physical inactivity, smoking, drug or alcohol abuse, and cardiovascular history, were based on recall and, therefore, may not have been defined precisely. Moreover, there was no information accessible to determine changes in these risk factors throughout follow-up. The composite end point of dementia, Alzheimer disease, and cognitive impairment neglects the different types of cognitive disorders, but because of limited numbers, it was not possible to assess these categories of cognitive impairment separately.

CONCLUSION

Exercise capacity is independently and inversely associated with the onset of dementia, Alzheimer disease, and cognitive impairment even after correction for multiple cardiovascular risk factors, such as smoking and physical inactivity. The inverse association between fitness and cognitive impairment provides an additional impetus for health care providers to promote physical activity.

Abbreviations and Acronyms: **ACE** = angiotensin-converting enzyme; **BMI** = body mass index; **CVD** = cardiovascular disease; **HR** = hazard ratio; **MET** = metabolic equivalent

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