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Association between physical fitness, cardiovascular risk factors, and Parkinson's disease

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Abstract

Objective: Exercise is a cornerstone of therapy for Parkinson's disease. This study addressed the association between physical fitness and the onset of Parkinson's disease and association with cardiovascular risk factors.

Patients and methods: Male veterans ($N = 7347$, 59.0 ± 11.2 years) from the Veterans Exercise Testing Study cohort were evaluated. Physical fitness was measured objectively by maximal exercise testing. Onset of Parkinson's disease was abstracted from the Veterans Affairs computerized patient records system.

Results: After a mean follow-up of 12.5 ± 6.3 years, a total of 94 (1.3%) developed Parkinson's disease. Incidence was 86 cases per 100,000 person-years. The strongest multivariate factors associated with incidence of Parkinson's disease were higher age (hazard ratio: 1.067, 95% confidence interval (CI): 1.043–1.093, $p < .001$), current smoking (hazard ratio: 0.511, 95% CI: 0.274–0.953, $p = .035$) and physical fitness (high *vs.* low: hazard ratio: 0.239, 95% CI: 0.079–0.725, $p = .011$). Compared with patients with no or only one of these risk factors, patients with two risk factors had a 3.7-fold ($p < .001$) increased risk for incidence of Parkinson's disease; those with all three risk factors had a 7.8-fold ($p < .001$) higher risk.

Conclusions: High physical fitness, current smoking and younger age were associated with a lower incidence of Parkinson's disease. These findings parallel those of several epidemiological studies focusing on physical activity and the onset of Parkinson's disease. Together, these observations provide strong support for recommending physical activity to diminish risk of Parkinson's disease.

Keywords

Parkinson disease, outcome study, physical fitness, environmental risk factors, epidemiology

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Introduction

Parkinson's disease is a neurodegenerative disorder characterized by dopaminergic cell loss through degeneration of substantia nigra.[1] This leads to limitations of the motor system which can be recognized as rigidity, tremor or postural instability.[2] The pathogenic mechanisms of Parkinson's disease remain unknown, but its etiology involves both genetic and environmental factors; effective disease-modifying therapies currently remain elusive.[2,3]

Many case–control studies and few smaller prospective cohort studies have examined the effects of multiple potential risk factors including environmental exposure, caffeine, smoking, diet and inflammation and their interactions with Parkinson's disease incidence.[2,4–8] Unfortunately, the majority of these studies have methodological limitations, including recall bias, inaccurate assessment of Parkinson's disease, reverse causality and their retrospective nature in general.[2]

Another modifiable risk factor for Parkinson's disease of particular interest is physical activity. Several studies,[9–15] including a recent meta-analysis,[11] provide

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compelling evidence for an inverse association between physical activity and the onset of Parkinson's disease.[3] However, studies have not been entirely consistent; all used questionnaires, which are prone to recall error and overestimation of physical activity, and there are inconsistencies in methods and terminology used. For example, these studies have interchangeably used the terms ''physical activity'' (behavior) and ''physical fitness'' (attribute) and used different protocols, interventions, and outcome measures, which has limited the interpretation of previous results.[14]

Therefore, the aim of the current study was to explore the association between objective measures of physical fitness and Parkinson's disease.

Patients and methods

Study subjects

The study population consisted of 7347 male veterans (59.0 ± 11.2 years) from the Veterans Exercise Testing Study (VETS) cohort.[16] As described previously,[16,17] the VETS began in 1987 and is an ongoing, prospective evaluation of veteran subjects referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. Historical information was recorded at the time of the exercise test.[17] Risk factors and outcomes were abstracted from the Veterans Affairs computerized medical records system. Smoking was categorized as never, former, and current smoker. Dyslipidemia was defined as a cholesterol level >220 mg/dL, statin use, or both. Exercise capacity was expressed as metabolic equivalents (METs) estimated from peak treadmill speed and grade.[18] 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[19] and were classified as physically inactive.

Outcomes

Parkinson's disease was determined according to ICD-9-code CM 332.0 in medical records. Outcomes were recorded as of February 2017.

Data analyses

All descriptive data are expressed as mean ± standard deviation and categorical variables are presented in absolute numbers or as percentages as appropriate. Independent variables associated with the onset of Parkinson's disease were estimated using univariate Cox proportional hazards analysis. All variables that exhibited a significant univariate association were tested in a multivariate model. Receiver operating characteristic (ROC) curves were used to derive the cut-off-value for highest sensitivity and specify for a given independent parameter. Kaplan–Meier survival curves were generated to illustrate the association between risk factors and onset of Parkinson's disease. For all analyses, a probability value of $p<.05$ was considered statistically significant. All analyses were performed using SPSS 23.0 software (IBM Inc., Armonk, New York, USA).

Results

Patient characteristics are displayed in Table 1. After a mean follow-up of 12.5 ± 6.3 years, a total of 94 subjects (1.3%) developed Parkinson's disease. An overview of the prevalence of Parkinson's disease by age

Table 1. Study characteristics of the sample.

	Whole study group $N = 7347$
Age, years	59.0 ± 11.2
BMI, kg/m^2	28.8 ± 5.2
Follow-up, years	12.5 ± 6.3
Exercise capacity, METs	8.5 ± 3.5
Exercise capacity	
Low, < 8 MET	3685 (50.2%)
Medium, 8–12 MET	2534 (34.4%)
High, >12 MET	1128 (15.4%)
Risk factors	
History of CVD	1902 (25.9%)
History of hypertension	3847 (52.4%)
History of dyslipidemia	2985 (40.6%)
Smoking	
Never	2470 (33.6%)
Former	2826 (38.4%)
Current	2051 (28.0%)
Physically inactive	2635 (35.9%)
Medications	
Beta blockers	1613 (22.0%)
ACE inhibitors	1442 (19.6%)
Antihypertensive agents	1378 (18.8%)
Diuretics	403 (5.5%)
Statins	874 (11.9%)

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

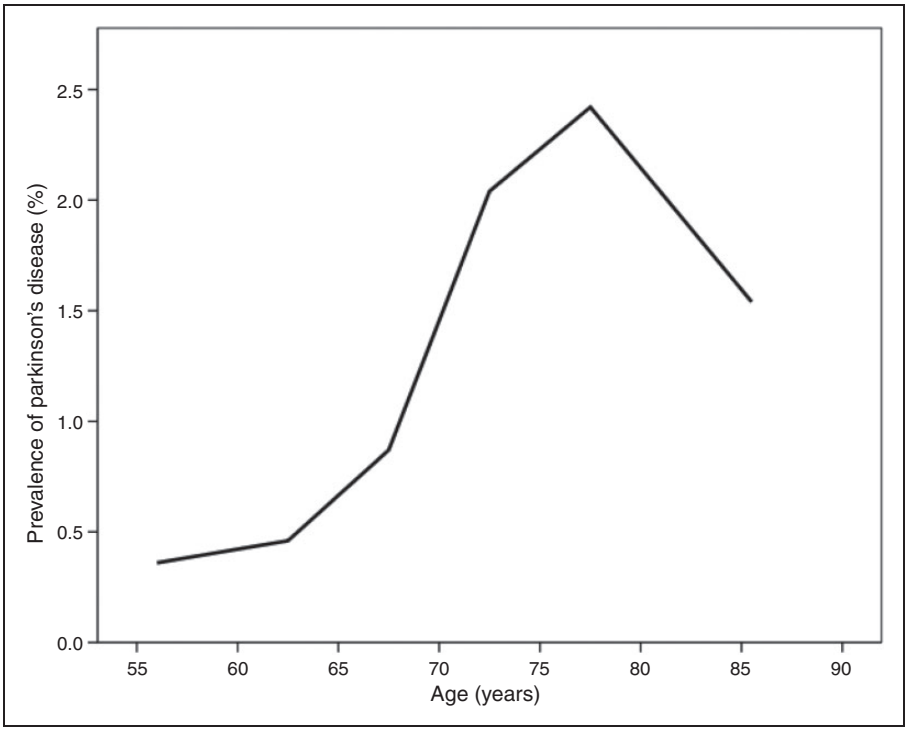

Figure 1. Prevalence of Parkinson's disease by age.

groups is shown in Figure 1. Overall incidence rate was 86 cases per 100,000 person-years.

Univariate risk factors associated with the incidence of Parkinson's disease were higher age at the time of the test (hazard ratio: 1.078, 95% confidence interval (CI): 1.055–1.101, $p < .001$) and dyslipidemia (hazard ratio: 1.540, 95% CI: 1.022–2.320, $p = .039$). Current smoking (hazard ratio: 0.369, 95% CI: 0.200–0.680, $p = .001$) and higher fitness (hazard ratio: 0.895, 95% CI: 0.841–0.952, $p < .001$) were inversely associated with risk of Parkinson's disease. Each 1-MET increase in exercise capacity conferred a 10.5% reduction in risk of Parkinson's disease in the univariate model (Table 2). In the final multivariate analysis (Table 2) higher age at the time of the test (hazard ratio: 1.067, 95% CI: 1.043–1.093; $p = .011$), high fitness (hazard ratio: 0.239, 95% CI: 0.079–0.725, $p = .035$) and current smoking (hazard ratio: 0.511, 95% CI: 0.274–0.953, $p = .035$) remained significantly associated with the onset of Parkinson's disease.

ROC analysis revealed that an age >59.2 years had the highest sensitivity and specificity for predicting the onset of Parkinson's disease. For illustration, a cut-off value of 60 years was chosen. In the ROC curve from physical fitness there were two peaks: one at 11.6 MET and another one at 8.1 MET. Therefore, the fitness level of veterans with a MET higher than 12 was classified "high", those with 8–12 MET "medium" and those with < 8 MET "low".

Kaplan–Meier curves for onset of Parkinson's disease stratified by risk factors at baseline from the final multivariate model (age 60 years or older, physical fitness < 12 MET, not a current smoker) are shown in Figure 2.

Compared with veterans with no or only one risk factor, veterans with two risk factors had a 3.7-fold (95% CI: 1.810–7.472, $p < .001$) increased risk for the onset of Parkinson's disease; in those with all three risk factors the relative risk was 7.8-fold (95% CI: 3.939–15.564, $p < .001$).

Discussion

We observed that higher physical fitness reduces the risk of Parkinson's disease after adjustment for age and smoking. The prevalence and incidence rates of Parkinson's disease across the age spectrum that we observed were consistent with other studies.[2,20] Small differences in prevalence between the current and previous studies are likely the result of environmental exposures and distribution of susceptibility genes. Similar to previous studies, decline in prevalence and incidence in the higher age groups (Figure 1) has been suggested to be due to artifacts related to higher diagnostic uncertainty due to comorbid disorders, diagnostic nihilism, and selective loss to follow-up.[2]

Table 2. Independent predictors in the univariate and multivariate Cox proportional hazard analysis models for Parkinson's disease in the 7347 male veterans.

	Bivariate model		Multivariate model	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age, years	1.078 (1.055–1.101)	<**.001**	1.067 (1.043–1.093)	<**.001**
BMI, kg/m^2	0.982 (0.942–1.023)	.379		
Physical fitness, METs	0.895 (0.841–0.952)	<**.001**	1.065 (0.982–1.155)	.127
Physical fitness				
Low, reference	1		**1**	
Medium	0.630 (0.405–0.981)	**.041**	0.667 (0.381–1.166)	.156
High	0.222 (0.100–0.493)	<**.001**	0.239 (0.079–0.725)	**.011**
Physically inactive	1.088 (0.692–1.710)	.716		
Smoking				
Never, reference	1		1	
Former	0.850 (0.536–1.347)	.489	0.762 (0.480–1.209)	.248
Current	0.369 (0.200–0.680)	**.001**	0.511 (0.274–0.953)	**.035**
History of CVD	1.210 (0.770–1.902)	.409		
History of dyslipidemia	1.540 (1.022–2.320)	**.039**	1.392 (0.922–2.102)	.116
History of hypertension	1.131 (0.753–1.669)	.522		

BMI: body mass index; MET: metabolic equivalent; CVD: cardiovascular disease; CI: confidence interval

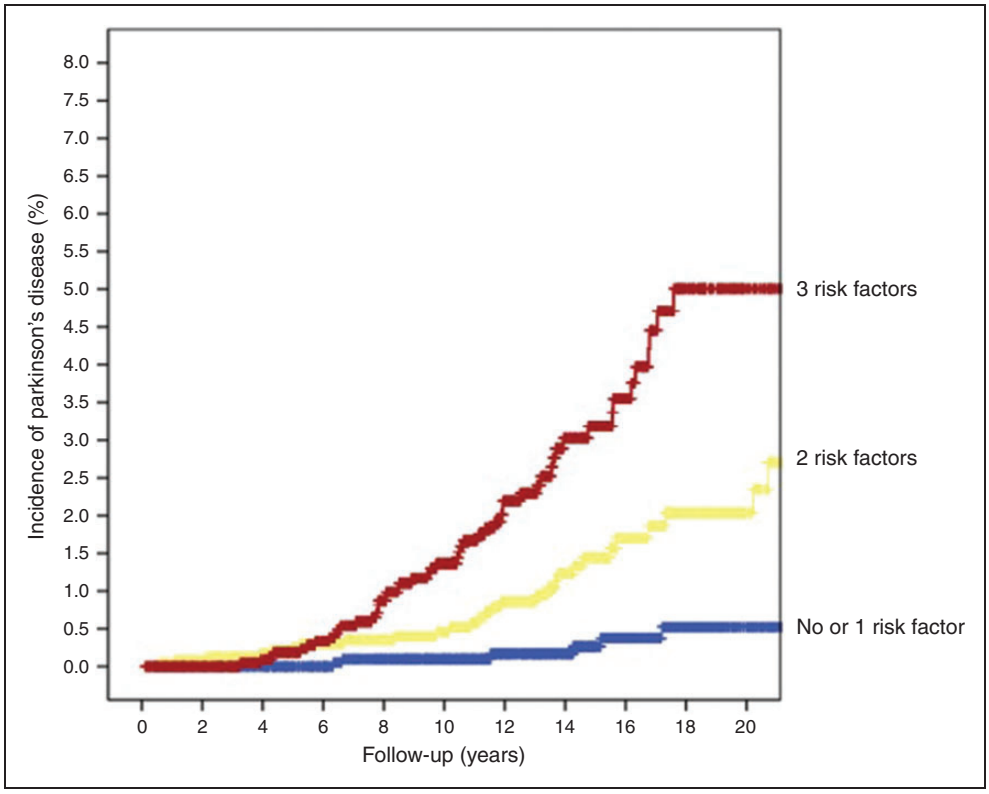

Figure 2. Incidence of Parkinson's disease according to the risk factors >60 years, no smoking, and low physical fitness.

Physical fitness

Several recent studies have addressed the relationship between physical activity pattern and incidence of Parkinson's disease.[9–15] Although the results are not entirely uniform, there is a consistent trend toward an inverse association between level of physical activity and Parkinson's disease incidence. A tremendous shortcoming of these studies is that all of them estimated physical activity using a self-reported questionnaire.[21] Recall bias, in term of types, duration and intensity of activity, is a major drawback, particularly in a condition such as Parkinson's disease in which the incidence is relatively rare. Furthermore, the measure of physical activity is inconsistently captured because some studies did distinguish between household, leisure-time and occupational physical activity and some not.[3,9,11]

Our data support this inverse association using a more robust, objective measure – physical fitness.[22] Although physical activity and fitness are often used interchangeably, they are different entities; physical activity is a behavior that develops fitness, an attribute. That is important particularly when referring to vigorous physical activity and Parkinson's disease risk,[10,12,23] given that self-reported physical activity tends to overestimate physical activity.[21] Our results support the findings of Chen[12] and Xu[10] and their coworkers and the meta-analysis from Yang et al.[11] demonstrating that higher physical activity has a protective effect for Parkinson's disease. The current findings extend these earlier studies, underscoring an inverse association between objectively measured fitness and incidence of Parkinson's disease.

Potential explanations for the beneficial effects of exercise on Parkinson's disease are provided by animal models. By increasing brain blood flow, exercise may facilitate neuroplasticity by angiogenesis, cell growth, and neuroprotection as well as enhance synaptic function that restores a degree of basal ganglia circuitry.[1,24,25] Tillerson and colleagues[26,27] reported that exercise attenuated the effects of the neurotoxins 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) after nigrostriatal damage. Brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in the striatum have been shown to increase in rats following chronic exercise.[28] However, the extent to which these mechanisms contribute to the neuroprotective effects of exercise in humans is unclear.

Interventional studies in humans with Parkinson's disease have shown that vigorous treadmill exercise elevates striatal dopamine D2 receptor binding potential and also improves postural control.[29] Intense exercise also increases blood uric acid concentration,[30] a natural antioxidant that reduces oxidative stress and diminishes Parkinson's disease risk.[8] Together, these findings provide a strong impetus for recommending regular exercise, particularly of a vigorous nature,[23] to diminish Parkinson's disease risk. However, in the context of exercise, the potential of volume and intensity on physical fitness should not be neglected since vigorous exercise has lower volume but higher intensity, and moderate exercise vice versa.

Smoking

Cigarette smoking is probably the most studied modifiable risk factor for Parkinson's disease. Case–control as well as prospective cohort studies have yielded results similar to ours – a reduced risk of Parkinson's disease among smokers, former smokers and exposure to second-hand smoking.[2,31,32] Cigarette smoke contains a multitude of chemicals in addition to nicotine, but nicotine appears to be the agent with a neuroprotective effect. The pathway is not fully understood, but nicotine blocks monoamine oxidase-b (MAO-B), which is an enzyme that metabolizes dopamine.[33] In smokers, and even those exposed to second-hand smoke,[31,34] nicotine inhibits this metabolite, causing better survival of dopamine neurons, which appears to prevent Parkinson's disease or reduce the risk for Parkinson's disease, or both. Moreover, nicotine is an agonist to nicotinic acetylcholine receptors that mediate the neuroprotective effect of MOA-B.[6] Prospective studies in rodents have also reported that nicotine was partially protective against the neurotoxin MPTP, which plays a key role in MAO-B metabolism,[35] which inhibits dopaminergic neurons. Since the genesis and progression of Parkinson's disease is very slow, studies[4,32] that included duration, intensity, and cessation of smoking suggest that sustained, lifelong smoking is more beneficial than recent smoking and smoking volume.

Early randomized controlled trails with nicotine patches in patients with Parkinson's disease have recently begun.[36] However, treatment strategies with nicotine, either preventive or curative, raise an ethical debate in terms of whether its positive effects offset the well-known detrimental effects of nicotine on health.

Cholesterol and statin use

Although not significant in our final multivariate model, serum cholesterol, including the dietary component, and statin use have been of particular interest in studies on Parkinson's disease. There have been conflicting findings regarding whether there are beneficial, negative, negligible effects of cholesterol level and statin use on the onset of Parkinson's disease[5,37–39] Indeed, there are reasonable arguments on both sides since statins reduce neuroinflammation and confer protection

against Parkinson's disease in animal and cell models.[38] Cholesterol is involved in many biological functions, including cellular repair, and plays an important role in the central nervous system.[37] However, in research contexts, the cofounding effect and dynamic relationship between cholesterol levels and statin use has often been neglected.[38] Thus a possible rationale might be that the use of statins simply neutralizes the protective effects of high cholesterol. However, the interaction between cholesterol and cholesterol subfractions, the need for statins or statins themselves, as well as dietary behavior (dairy products and unsaturated fatty acids) are of interest because Parkinson's disease is a systemic disease and recent studies suggest that Parkinson's disease could have its origin in the gut.[6,40]

Conclusion

High physical fitness, current smoking and younger age were associated with a lower onset of Parkinson's disease; these findings confirm those of several epidemiological studies focusing on physical activity and onset of Parkinson's disease. Together, these findings provide a strong impetus for recommending exercise to diminish Parkinson's disease risk. However, further studies are needed to clarify intensity, duration and type of exercise, and how exercise mediates traditional cardiovascular risk factors and their association with Parkinson's disease.

Limitations

The diagnosis of Parkinson's disease is based solely on ICD-codes and no further objective measurements or other data were available. It cannot exclude that in different groups of patients the diagnosis is made at different stages of the disease, thereby changing the apparent incidence. One drawback, for example, may be that fitter individuals take longer to present with symptoms because of better compensating mechanisms and postponed diagnosis of Parkinson's disease.

Due to the extended period of recruitment of study participants, era effects in diagnosing Parkinson's disease during follow-up might have biased the data as well.

Parkinson's disease has a very slow progression and we cannot entirely exclude the possibility that subclinical Parkinson's disease was present at baseline testing. However, Figure 2 suggests that almost all of the cases occurred five years and beyond after baseline testing. Dyslipidemia is a condition that has in common high cholesterol, statins, or both, and thus it is not possible to adjust for these potentially confounding effects. In addition, our findings apply only to men, but determining whether fitness has a gender effect will be important in developing future prevention and intervention strategies for Parkinson's disease.[3] Finally, METs were calculated from treadmill speed and grade, an indirect measure of fitness; thus, further research is needed to confirm these findings using directly measured peak oxygen uptake.

Author contribution

JMü was responsible for sampling, analyzing and interpretation of the data and drafted the first version of manuscript. JMy was responsible for conception and design of the study, sampled, analyzed and interpreted the data and gave important input for drafting and revising the manuscript

Declaration of conflicting interests

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