Physical activity and the risk of Parkinson disease

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Abstract—Objective: To investigate whether greater physical activity is associated with a lower risk of Parkinson disease (PD). Methods: The authors prospectively followed 48,574 men and 77,254 women who provided information on physical activity in 1986 or in early adulthood. During the follow-up, a total of 252 (male) and 135 (female) incident PD cases were identified. Results: In men, greater baseline physical activity was associated with a lower PD risk; compared with the lowest quintile, the multivariate relative risk (RR) of PD for the highest quintile was 0.7 (95% CI 0.5 to 1.1; p value, test for trend = 0.007), and the inverse association was still present after excluding the first 10 years of follow-up (RR = 0.5; p value, test for trend = 0.02). Further, strenuous exercise in early adult life was also inversely related to PD risk in men: compared with men who regularly exercised ≤2 months/year, those with ≥10 months of strenuous exercise had a 60% lower PD risk (RR = 0.4; p value, test for trend = 0.005). In women, physical activity assessed at baseline was not related to PD risk, whereas strenuous exercise in early adulthood tended to be inversely related to PD risk later in life (highest vs lowest categories, RR = 0.5, 95% CI 0.2 to 1.4; p value, test for trend = 0.06). Conclusion: This study suggests either that higher levels of physical activity may lower the risk of Parkinson disease (PD) in men or that men predisposed to PD tend to avoid strenuous physical activity in their early adult years.

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Clinical investigations suggest that physical therapy may improve the physical capability and quality of life among patients with Parkinson disease (PD). In rodent models of PD, forced exercise following the administration of 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine spared striatal dopamine and alleviated behavioral abnormalities. Interestingly, similar effects could also be achieved if the forced exercise was carried out prior to the treatment, suggesting that physical exercise may be neuroprotective. However, whether greater physical activity decreases the risk of developing PD in human has been considered in only a few case-control studies, and the results were inconsistent. Therefore, we prospectively investigated the association between physical activity and the risk of PD in two large cohorts of US men and women: the Health Professionals Follow-Up Study (HPFS) and the Nurses’ Health Study (NHS).

Methods. Study population. The HPFS cohort was established in 1986 when 51,529 male health professionals ages 40 to 75 responded to a mailed questionnaire that asked detailed questions on disease history, dietary habits, and lifestyle practices, including leisure-time physical activities. The NHS was established in 1976 when 121,700 registered nurses ages 30 to 55 years answered a similar questionnaire. After baseline, both cohorts were followed by means of biennial questionnaires to update information on lifestyle practices and to ascertain whether major medical events had occurred. The overall response rate is >94% in the HPFS, and the NHS follow-up has been 95% of potential person-years in the overall cohort. A question on lifetime occurrence of PD was first included in the 1988 (HPFS) and 1994 (NHS) questionnaires and subsequently updated every 2 years. We used the date of returning of the 1986 questionnaire as baseline in the analyses for both cohorts as detailed information on physical activity was not elicited in NHS until 1986. Participants with PD, stroke, or cancer (other than nonmelanoma skin cancer) at baseline or with missing values on baseline physical activity were excluded from the analyses. We followed 48,574 eligible men and 77,254 women from baseline to the date that the first PD symptoms were noticed, the date of stroke diagnosis or death, or the end of the follow-up (January 31, 2000, in men and May 31, 1998, in women), whichever occurred first. These studies were approved by the Human Subjects Committees at the Harvard School of Public Health (HPFS) and Brigham and Women’s Hospital (NHS).

Physical activity assessment. In 1986, participants in both cohorts were asked to report the average time they spent per week on each of the following activities over the previous year: walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, squash or racket ball, and calisthenics or rowing (HPFS) or calisthenics/aerobics/aerobic dance/rowing machine (NHS). For each activity, we asked the number of miles of stairs climbed per day with five categories ranging from 0 to ≥11 hours. In addition, we also asked the number of flights of stairs climbed per day with five categories ranging from ≤2 to >15. Similar questions were asked every 2 years during the follow-up, with the only exception of the 1990 NHS questionnaire, in which most activities were not asked. Based on these individual activities, we calculated total physical activity in metabolic equivalent tasks (METs) by multiplying the hours spent per week on each activity by its typical energy expenditure requirements. Activities that required sixfold or more increase from resting metabolic rate (≥6 METs) were defined as...
vigorou and those that required fewer METs as moderate. According to this definition, moderate activities included walking or hiking outdoors and stair climbing, whereas the remaining activities were classified as vigorous. The validity of physical activity assessed in these questionnaires was examined among 238 HPFS participants who also completed four 1-week activity diaries at four time periods corresponding to different seasons; a subset of these participants also completed a step test. Vigorous activity assessed by the questionnaire was positively correlated with that from the activity diaries (correlation coefficient, r = 0.58) and negatively correlated with resting pulse (r = −0.45) and postexercise pulse (r = −0.41). Information on early-life physical activity was also collected in both cohorts. In the 1992 HPFS questionnaire, we asked participants on average how many months every year they spent ≥ 2 days/week in certain strenuous exercises such as swimming, soccer, hockey, basketball, cycling, and running. The question was asked separately for ages at high school, college, and 30 to 40 years, and five answers were allowed (months/year): 0, 1 to 3, 4 to 6, 7 to 9, and 10 to 12. Overall level of early-life strenuous activity was further derived by averaging the values at all three life periods. In the NHS cohort, a similar question was included in the 1988 questionnaire to assess the frequency of strenuous exercises during ages 18 to 22 only.

Usual adult height was asked in HPFS in 1986 and NHS in 1976, and information on smoking status, weight, menopausal status, and postmenopausal hormone use was collected both at baseline and in each of the biennially updated questionnaires. Body mass index was calculated as weight in kilograms divided by height squared in meters. Dietary assessments, including the consumption of coffee and caffeine-containing drinks, were conducted at baseline and every 4 years during the follow-up with validated food frequency questionnaires.

**PD case ascertainment.** Ascertainment of the PD cases in these cohorts has been previously described. In brief, after obtaining permission from participants who reported a new diagnosis of PD, we asked the treating neurologist (or internist, if the neurologist was not available) to complete a questionnaire to provide his/her judgment on the certainty of the diagnosis or to send a copy of the medical record. A case was confirmed if a diagnosis of PD was considered definite or probable by the treating neurologist or internist or if the medical record included either a final diagnosis of PD made by a neurologist or evidence at a neurologic examination of at least two of the three cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by the investigators, blind to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 82.3% of the cases, by review of the medical records in 3.1% of the cases, and by the treating internist without further support in the remaining 14.6% of the cases.

**Statistical analysis.** We used quintiles of baseline physical activity as the major exposure variables and related them to the risk of PD during the follow-up. Relative risks (RRs) were calculated by dividing the incidence rate of PD in each of the higher quintile categories by the corresponding rate in the lowest quintile, adjusting for age in 5-year increments and smoking status (never smoker, past smoker, or current smoker: 1 to 15 cigarettes/day) with the Mantel–Haenszel method. Multivariate RRs were derived from the Cox proportional hazards model that controlled for age at baseline (categorized in tertiles), sex, race, body mass index (continuous), smoking status (never smoker, past smoker, or current smoker: 1 to 15 cigarettes/day), caffeine intake (quintiles), alcohol consumption (men: 0 to 1 to 9.9, 10 to 19.9, 20 to 29.9, or ≥ 30 g/day; women: 0 to 1 to 4.9, 5 to 9.9, 10 to 14.9, or ≥ 15 g/day), lactose intake (quintiles), and body mass index (< 23, 23 to 24.9, 25 to 26.9, 27 to 29.9, ≥ 30 kg/m²).

The p for linear trend was calculated by using the median of each quintile category as a continuous variable in the Cox model. For all RRs, we calculated 95% CIs, and all p values were two-tailed.

As an early preclinical decline in physical activity among PD patients could cause a spurious inverse association between exercise levels and PD risk, we performed lag analyses by excluding the first 4, 6, 8, and 10 years of follow-up in men. In women, we excluded only the first 4 years of follow-up because of fewer PD cases after that. We also excluded the period of change in the Cox models. For all RRs, we calculated 95% CIs, and all p values were two-tailed.

We identified a total of 252 male and 135 female incident cases of PD during the follow-up. The average age when the first symptoms of PD were noticed was 69.5 ± 8.5 years for men and 64.7 ± 6.1 years for women. In men, overall physical activity was inversely associated with PD risk (see Table E1 on the Neurology Web site at www.neurology.org). Compared with men in the lowest quintile, those in the highest quintile had a 30% lower PD risk (RR = 0.7; 95% CI 0.5 to 1.1; p value, test for trend = 0.007). Further analyses showed that greater vigorous activity, but not moderate activity, was related to lower risk of PD in men; the multivariate RR comparing men in extreme quintiles of vigorous activity was 0.5 (95% CI 0.3 to 0.9; p value, test for trend = 0.004). Physical activity remained inversely related to PD risk in the lag analyses: After excluding the first 10 years of follow-up, the RRs between PD risk and physical activity were 0.5 (95% CI 0.3 to 0.9; p value, test for trend = 0.004) in men and 0.7 (95% CI 0.4 to 1.1; p value, test for trend = 0.11) in women.
extreme categories were 0.5 (95% CI 0.2 to 1.1; p value, test for trend = 0.02) for total physical activity and 0.4 (95% CI 0.2 to 1.2; p value, test for trend = 0.02) for vigorous activity. Similar results were also obtained in the 4-, 6-, and 8-year lag analyses. Subgroup analyses in men by age, smoking, and caffeine intake revealed no significant differences across strata.

In men, levels of strenuous physical activity in high school, college, and ages 30 to 40 predicted the risk of PD in later life (see table E-2). With use of the average level of strenuous exercise over these life periods as an overall indicator, men who spent ≥10 months/year in strenuous activities had 60% lower PD risk than men who spent <2 months (95% CI 0.2 to 0.7; p value, test for trend = 0.005). The RRs were minimally changed when we included only the 1992 to 2000 follow-up in our analyses or further adjusted for vigorous physical activity reported in 1986 (RR = 0.5; 95% CI 0.3 to 0.8; p value, test for trend = 0.02).

Neither total nor vigorous physical activity was inversely associated with PD risk in women. Strenuous exercise at ages 18 to 22 was nonsignificantly associated with lower PD risk: compared with the reference group (0 month/year), the RRs were 1.2 for 1 to 3 months, 0.9 for 4 to 6 months, 0.4 for 7 to 9 months, and 0.5 (95% CI 0.2 to 1.4) for 10 to 12 months of strenuous exercises (p value, test for trend = 0.06).

Significant declines in physical activity over time in excess of those attributable to aging and smoking were observed in both men and women (figures 1 and 2). In men, consistent with the Cox proportional hazard analysis, a significantly lower level of physical activity was already present 12 years before the diagnosis, and a sustained decrease was observed after the diagnosis and persisted throughout the follow-up. In women, the decline began at approximately 2 to 4 years prior to the diagnosis but slowed down after 2 years from the diagnosis.

**Discussion.** In this large prospective study, greater physical activity was associated with a lower risk of PD in men. A 50% risk reduction was observed when comparing men in the highest category of vigorous physical activity vs those in the lowest. In women, baseline physical activity was not related to the risk of PD. Not surprisingly, the level of leisure physical activity began to decrease several years before the diagnoses in both men and women.
Few epidemiologic studies have examined the association between physical activity and the risk of developing PD. In a nested case-control study with 94 PD cases, moderate physical activity was found to be associated with a nonsignificantly lower risk of PD in men. However, in a small retrospective case-control study (32 cases), the adult physical activity of PD patients was not different from that of control subjects up to the sixth decade of life. In another retrospective study, significantly less physical exercise was reported by young-onset PD cases (n = 30) than by controls or late-onset cases (n = 60). The inconsistency of these previous studies probably results from their inaccurate measurements of physical activity and potential recall bias, in addition to small sample sizes. None of these studies used a structured and validated questionnaire in assessing physical activity. Potential recall bias, in the case of PD, could be substantial because patients often experience cognitive decline and tend to gradually lose exercise capacities prior to the diagnosis.

In contrast to these previous investigations, both the HPFS and the NHS are large prospective cohorts with long follow-up periods. The data were prospectively collected, and lag analyses were conducted to examine the potential effects of preclinical physical decline on the results. We examined both baseline physical activity and early-life strenuous activities at different life spans in men and found similar results. The inverse association between physical activity and PD risk in men was further supported by our analyses that men with PD were consistently less physically active than men without PD up to 12 years prior to the diagnosis. In both cohorts, participants were asked detailed questions on different leisure-time physical activities. The exposure assessments have been previously validated and were predictive of future risks of coronary heart disease, stroke, diabetes, and cancer. Because of the prospective design, any misclassification of exposure variable would most likely be nondifferential and therefore would cause an underestimation of the inverse association between physical activity and PD risk in men.

The fact that both baseline and early-life exposure analyses revealed inverse associations between vigorous or strenuous exercise and risk of developing PD is consistent with the hypothesis that high level of physical exercise may lower PD risk. In the rat model of PD, forced exercise prior to 6-OHDA treatment induced a significant increase of glial-derived neurotrophic factor that has neuroprotective effects for dopaminergic neurons. Physical exercise can also promote secretion of brain-derived neurotrophic factor and other growth factors in the CNS that in turn may contribute to the survival and neuroplasticity of dopaminergic neurons. Moreover, exercise decreases the ratio between dopamine transporter and vesicular monoamine transporter; a decrease in this ratio may lower the susceptibility of dopaminergic neurons to neurotoxins and reduce cytosolic dopamine oxidation. Finally, physical exercise may activate the dopaminergic system and increase dopamine availability in the striatum. Any of these or other mechanisms may be responsible for the beneficial effects of forced exercise in animal experiments; however, the relevance of these short-term animal findings to possible neuroprotective effects of leisure

Figure 1. Average physical activity of Parkinson disease (PD) cases as percentage of noncases at different time points before and after the diagnosis in men, adjusting for age, age squared, and smoking status for each time period. The sample size at each time point ranges from 48 to 228. The reference line represents the average values of individuals without PD.

Figure 2. Average physical activity of Parkinson disease (PD) cases as percentage of noncases at different time points before and after the diagnosis in women, adjusting for age, age squared, and smoking status for each time period. The sample size at each time point ranges from 57 to 115. The reference line represents the average values of individuals without PD.
physical exercise in human PD pathogenesis remains to be established.

The preclinical decline of physical activity reflects the insidious nature of the disease and unrecognized physiopathologic changes that may limit the patients' capability to tolerate vigorous exercises. Enhanced fatigue is commonly seen among PD patients and is even one of the presenting symptoms of the disease. Fatigue in PD may be associated with a generalized mitochondrial dysfunction. Alternatively, fatigue may reflect the underlying progressive loss of dopaminergic neurons in the CNS, which develops years before the disease diagnosis. The observation of preclinical changes of physical activity complements our previous findings that PD patients tended to lose weight 2 to 4 years prior to disease diagnosis despite a simultaneous increase in energy intake. Whether the apparent paradox of weight loss in PD patients is related to its symptoms or implies an underlying inefficiency of energy metabolism merits further investigation.

Several limitations should be considered in interpreting the results. For PD diagnoses, we have to rely on the judgments of patients' neurologists. Because of the lack of independent pathologic confirmation, it is possible that some cases have been misdiagnosed. However, as we have discussed in our previous publications, the potential bias from this source is likely to be small. It is also possible that a few participants with PD never reported the disease on the questionnaires. However, this potential underreporting would result in a spurious inverse association between physical activity and PD only if it were largely restricted to the more active individuals, which seems highly unlikely. It is possible that physically active individuals are more health conscious and more likely to have routine examinations. If this is the case, the inverse association between physical activity and PD risk in men may have actually been underestimated. The information on early-life strenuous physical activities was retrospectively collected and therefore was subject to memory loss and recall bias. However, the fact that the analyses of 1992 to 2000 follow-up, which included only cases with onset after the assessment of early-life physical activity, generated almost identical results as the 1986 to 2000 follow-up suggests that recall bias was minimal. PD is characterized by the progressive loss of dopaminergic neurons and may have a long latency period. Although results from both lag analyses and the analyses of early-life physical activity argue against the possibility of reverse causality, we cannot exclude the possibility that those individuals predisposed to the development of PD already had a tendency to refrain from vigorous physical activities during their early adulthood. The participants of our cohorts are not random samples of US men and women. Therefore, the levels of physical activity in these cohorts may not be representative of the general US population.

For women, physical activity was not associated with a statistically significant increase or decrease in PD risk. Nevertheless, the risk of PD was substantially lower among women who reported strenuous exercise during early adulthood. The lack of statistical significance could be due to the fact that analyses in women were based on relatively small numbers of cases, only about half that of men, and thus were more affected by random variations. The statistical power was further reduced by the lower intensity of physical exercise in women. Nevertheless, gender differences in risk factors for PD have been previously reported and may reflect some still unknown aspects of the pathogenesis of this disease. Further large prospective investigations are needed to replicate these findings and to explore and better understand the meaning of this inverse association and the observed gender difference.

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References


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