Published in final edited form as:
Mov Disord. 2008 January ; 23(1): 69–74.

Recreational Physical Activity and Risk of Parkinson's Disease

Evan L. Thacker, SM[1], **Honglei Chen, MDPhD**[2], **Alpa V. Patel, PhD**[3], **Marjorie L. McCullough, ScD**[3], **Eugenia E. Calle, PhD**[3], **Michael J. Thun, MD**[3], **Michael A. Schwarzschild, MDPhD**[4], and **Alberto Ascherio, MDDrPH**[1,5,6]

1 *Department of Nutrition, Harvard School of Public Health, Boston, MA*

2 *Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC*

3 *Epidemiology and Surveillance Research Department, American Cancer Society, Atlanta, GA*

4 *Department of Neurology, Massachusetts General Hospital, Boston, MA*

5 *Department of Epidemiology, Harvard School of Public Health, Boston, MA*

6 *Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Abstract

Purpose—To investigate associations between recreational physical activity and Parkinson's disease (PD) risk.

Methods—We prospectively followed 143,325 participants in the Cancer Prevention Study II Nutrition Cohort from 1992 to 2001 (mean age at baseline = 63). Recreational physical activity was estimated at baseline from the reported number of hours per week on average spent performing light intensity activities (walking, dancing) and moderate to vigorous intensity activities (jogging/running, lap swimming, tennis/racquetball, bicycling/stationary bike, aerobics/calisthenics). Incident cases of PD (n = 413) were confirmed by treating physicians and medical record review. Relative risks (RR) were estimated using proportional hazards models, adjusting for age, gender, smoking, and other risk factors.

Results—Risk of PD declined in the highest categories of baseline recreational activity. The RR comparing the highest category of total recreational activity (men ≥ 23 metabolic equivalent task-h/wk [MET-h/wk], women ≥ 18.5 MET-h/wk) to no activity was 0.8 (95% CI: 0.6, 1.2; p trend = 0.07). When light activity and moderate to vigorous activity were examined separately, only the latter was found to be associated with PD risk. The RR comparing the highest category of moderate to vigorous activity (men ≥ 16 MET-h/wk, women ≥ 11.5 MET-h/wk) to the lowest (0 MET-h/wk) was 0.6 (95% CI: 0.4, 1.0; p trend = 0.02). These results did not differ significantly by gender. The results were similar when we excluded cases with symptom onset in the first four years of follow-up.

Conclusions—Our results may be explained either by a reduction in PD risk through moderate to vigorous activity, or by decreased baseline recreational activity due to preclinical PD.

Keywords

Parkinson's disease; epidemiology; cohort study; behavioral risk factors; physical activity

Corresponding author: Evan L. Thacker; address: 655 Huntington Ave., Bldg. 2, Boston, MA 02115; phone: (617) 432-1839; fax: (617) 432-2435; email: ethacker@post.harvard.edu.

Introduction

The results of prospective epidemiological studies suggest that physical activity may decrease the risk of Parkinson's disease (PD) among men, but the evidence remains preliminary and inconclusive.[1–3] Part of the difficulty in synthesizing the results of previous studies to generate conclusions is that the methods of exposure and outcome assessment have not been consistent. One study was based on self-reported participation in a variety of specific recreational activities,[1] while two studies relied mostly on self-reported participation in sports without identifying specific activities other than walking and stair climbing.[2, 3] Further, only one study was based on neurologist-confirmed incident PD cases,[1] whereas the others combined unconfirmed self-reports of PD incidence with cases identified solely from death certificates.[2, 3] Moreover, two of the three studies included only men,[2, 3] while the results of the one study including women suggested a gender difference.[1] Although the results of previous studies seem qualitatively similar—suggesting slightly lower PD risk among men with high activity levels—additional data from studies that are methodologically comparable to the largest and strongest of the published studies[1] would help to further evaluate the possibility that physical activity may protect against PD. Thus, we assessed the relationship between recreational physical activity and the risk of incident PD among men and women participating in an ongoing prospective study, the Cancer Prevention Study II Nutrition Cohort (CPS-II-N).

Methods

Study participants

The CPS-II-N, established from 1992 to 1993 as a subgroup of the larger 1982 CPS-II mortality cohort, includes 184,190 participants (86,404 men and 97,786 women) from 21 U.S. states who reported their medical histories, lifestyle characteristics, and dietary habits in response to a mailed baseline (1992–1993) questionnaire.[4] Participants had also reported their medical, lifestyle, and dietary information in 1982, at the inception of the larger mortality cohort. As previously described,[5] in the 2001 follow-up questionnaire, participants were asked whether they had ever been diagnosed with Parkinson's disease. 143,325 individuals (63,348 men and 79,977 women) returned the 2001 questionnaire and did not report having had a diagnosis of PD or symptoms of PD at the time of the 1992–1993 baseline questionnaire. Of these, 1,986 (1%) were missing data on baseline recreational physical activity, leaving 141,339 (62,471 men and 78,868 women) for analysis. The study was approved by the Human Subjects Committee at the Harvard School of Public Health and the Institutional Review Board at Emory University.

Physical activity assessment

In the baseline questionnaire, participants were asked to report the average time per week during the past year they had spent at the following recreational activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing. Possible responses for each activity were "none," "1–3 hours per week," "4–6 hours per week," and "7 + hours per week." Each activity was assigned an average metabolic equivalent task (MET) value, representing the ratio of energy used during the activity to energy used at rest. Walking and dancing were assigned the value of 3.5 METs; bicycling/stationary bike, 4 METs; aerobics/calisthenics, 4.5 METs; tennis or racquetball, 6 METs; jogging/running and lap swimming, 7 METs.[6] Average energy expenditure at each activity was calculated by multiplying the corresponding MET value by the number of hours per week engaged in the activity, using the values 0 for none, 1 for 1–3 h/wk, 4 for 4–6 h/wk, and 7 for 7 + h/wk.[7] Total recreational physical activity in MET-h/wk was calculated by summing the MET-h/wk values over all recreational activities. We also calculated MET-h/wk separately for light activity (walking and dancing) and for moderate to vigorous activity (bicycling/stationary bike, aerobics/calisthenics, tennis or racquetball, jogging/running, and lap swimming). In addition to reporting their participation in specific activities at baseline, participants were asked in the baseline questionnaire to report the average time per week they had spent doing the same activities at age 40. These data were also summarized as MET-h/wk of total, light, and moderate to vigorous recreational physical activity as described above.

Parkinson's disease case ascertainment

Participants who reported a diagnosis of PD on the 2001 questionnaire were recontacted to verify their reports, the date of symptom onset, and to request permission to contact their treating neurologists and obtain copies of their medical records. Of the 840 participants who reported PD, 677 (81%) gave permission for contacting their treating neurologists. Baseline total recreational physical activity was not associated with permission to contact treating neurologists, adjusting for age and gender (increase of one MET-h/wk, OR = 1.0; $p > 0.9$). Neurologists were sent requests for detailed diagnostic information, including date of symptom onset, and medical records. If we were unable to contact a participant's neurologist we sought information from his or her internist. Of the 677 reported cases for whom we sought diagnostic confirmation, we obtained completed diagnostic questionnaires or medical records for 648 (96%), and confirmed a diagnosis of PD in 588 of these (91%). Cases were confirmed if the diagnosis was considered clinically 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 upon a neurological assessment of at least two of the four cardinal signs of PD (with one being rest tremor or bradykinesia), a progressive course, and the absence of unresponsiveness to L-dopa or other features suggesting an alternative diagnosis. Alleged cases with complete diagnostic questionnaires or medical records who did not meet the above confirmation criteria were rejected and excluded from analyses. Medical records were reviewed by one of the authors (M.A.S.), a neurologist specializing in movement disorders. Of the confirmed cases, we excluded 175 with symptom onset before the baseline survey, retaining 413 with symptom onset after baseline. Of the 413 incident cases, 68% were confirmed by the treating neurologists or movement disorders specialists, 21% by the review of neurological medical records, and 11% by the treating internists or family physicians.

Statistical analyses

Each participant contributed person time to follow-up from the date of return of the 1992 questionnaire to August 31, 2001 or the date of onset of the first symptoms of PD. We performed analyses for recreational physical activity at baseline and at age 40, using gender-specific MET-h/wk categories. We derived the categories using SAS proc rank, however because the MET-h/wk values were clumped, rather than smoothly continuous, the categories were not uniformly sized quantiles. For analyses of total recreational physical activity, categories were created by combining the MET-h/wk from all recreational activities (light and moderate to vigorous) and dividing participants into five total activity MET-h/wk categories. Because the physiological effects of physical activity may depend on intensity, we also conducted separate analyses for light and moderate to vigorous activity. For analyses of light activity, participants who reported any amount of moderate to vigorous activity were excluded, and four categories were created for the remaining participants based on MET-h/wk from walking and dancing (numbers were too small for five categories). For analyses of moderate to vigorous activity, we combined the MET-h/wk from all moderate to vigorous activities (jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics) and divided participants into five moderate to vigorous activity MET-h/wk categories.

We obtained gender-specific relative risks of PD comparing each category of physical activity to the corresponding lowest category from age-stratified Cox proportional hazards models, using the date of PD symptom onset as the outcome for all models. We found no violations of the proportional hazards assumption using an interaction terms between age and total, light, and moderate to vigorous activity. Results for men and women were pooled using random effects models. Trends over total, light, and moderate to vigorous MET-h/wk categories were tested by including the category medians as continuous variables in Cox models. All Cox models were adjusted for age (months), pack years of smoking (none, < 10, 10–19, 20–29, 30–39, ≥ 40, missing), years since quitting smoking (never smoked, ≥ 25, 10–24, < 10 including current smokers, missing), alcohol intake (grams/day: men: < 1, 1–9, 10–19, 20–29, ≥ 30, missing; women: < 1, 1–4, 5–9, 10–14, ≥ 15, missing), caffeinated coffee intake (cups/day: none, < 1, 1, 2–3, 4–5, ≥ 6, missing), total caloric intake (kilocalories/day: gender-specific quintiles, missing), dairy intake (grams/day: gender-specific quintiles, missing), body mass index (< 23, 23–24, 25–26, 27–30, ≥ 30, missing), pesticide exposure (never, ever, missing), ibuprofen use (< 15 days/month, ≥ 15 days/month, missing), and level of education (did not complete high school, high school graduate, vocational/trade school or some college, college graduate, graduate school, missing). Data for all covariates were drawn from responses to the baseline questionnaire, except for caffeinated coffee intake, height for body mass index calculation, pesticide exposure, and level of education, which were absent from the 1992 questionnaire but were assessed in 1982 as part of the larger CPS-II mortality study.

We performed several secondary analyses of the relationship between recreational physical activity and PD. We excluded PD cases with onset during the first four years of follow-up to see whether the results could have been influenced by declines in activity due to preclinical PD. To account for the possibility of underdiagnosis of PD, we also ran models in which we counted as cases the participants who reported PD but did not give permission to contact their neurologists for diagnostic confirmation. In additional models, we eliminated confounding by smoking by restricting the cohort to never smokers. Finally, we examined individual recreational activities for associations with PD by treating the MET-h/wk for individual activities as continuous variables.

Results

About 90% of participants reported engaging in recreational physical activity at baseline. Of these, 56% undertook only light physical activity, 39% reported a combination of light and moderate to vigorous activity, and 5% took part only in moderate to vigorous physical activity. The activities most commonly reported were walking (83% of men, 87% of women), bicycling/stationary bike (22% of men, 21% of women), and aerobics/calisthenics (11% of men, 16% of women). Mean total recreational physical activity was 13.5 MET-h/wk among men and 12.2 MET-h/wk among women. Men in the highest gender-specific category of total activity had a median of 28 MET-h/wk of activity, corresponding to about 8 hours of walking, 6 hours of aerobics, or 4 hours of lap swimming per week. For women in the highest gender-specific category of total activity, the median was 25 MET-h/wk, equivalent to about 7 hours of walking, 5.5 hours of aerobics, or 3.5 hours of lap swimming per week. Age-standardized means and proportions of variables for which we adjusted our relative risk estimates are available online (Supplemental Material Table S1). The mean age of participants at baseline was 63 years.

Clinical PD was confirmed in 413 individuals, of whom 409 (264 men and 145 women) had valid data on baseline physical activity. The mean age at symptom onset was 70.5 years in men and 70.0 years in women. Rest tremor was documented in 75% of cases, bradykinesia in 83%, rigidity in 73%, and postural instability in 42%. In multivariate-adjusted models of men and women combined, participants in the highest category of total recreational physical activity had a marginally significant, slightly lower risk of PD than participants in the lowest (RR = 0.8 [0.6, 1.2]; p for trend = 0.07) (Table). This association was entirely due to moderate to vigorous activity. Whereas no relation was found between the categories of light activity and

PD risk, participants in the highest category of moderate to vigorous activity (with or without light activity) had a 40% lower risk of PD than participants reporting no moderate to vigorous activity (RR = 0.6 [0.4, 1.0]; p for trend = 0.02). In gender-specific models, the lower risk of PD in the highest category of total recreational physical activity was apparent only among men. Lower risk of PD was observed for the two highest categories of moderate to vigorous activity among men; however, in women the risk was lower only in the highest category (Table).

In secondary analyses, we obtained similar results when we excluded the first four years of follow-up, included unconfirmed PD cases (participants who reported PD but did not grant permission to contact their neurologists for diagnostic confirmation), or restricted the cohort to never smokers (results available online, Supplemental Material Table S2). We did not observe significant associations between MET-h/wk of individual recreational activities and PD risk (data not shown). These analyses, however, lacked statistical power because only small percentages of participants reported engaging in most individual activities, especially those with the highest MET values. Finally, we found no relation between PD risk and total recreational physical activity at age 40 (highest category vs. no activity, RR = 0.9 [0.5, 1.7]; p for trend = 0.80) or moderate to vigorous activity (with or without light activity) at age 40 (highest category vs. none, RR = 1.1 [0.8, 1.5]; p for trend = 0.55).

Discussion

Our results provide evidence that moderate to vigorous physical activity may confer protection against the onset of Parkinson's disease in both men and women. Men and women in our study in the highest baseline categories of moderate to vigorous activity, such as bicycling, aerobics, or tennis, had the lowest risk of PD during follow-up. On the other hand, risk among participants who reported only light activity at baseline, such as walking or dancing, was similar to that of individuals who reported no activity at all. Moderate to vigorous activity at age 40 was not associated with PD risk.

An important concern in interpreting the results of the present study is the possibility of a spurious inverse association between physical activity and PD risk due to an effect of early, pre-symptomatic PD on physical activity (reverse causation). In our study, the RR estimates were consistent over time and did not materially change after excluding the first four years of follow-up, providing some evidence against reverse causation, but a longer period of follow-up would help further address this possibility. Also, confounding by unmeasured factors cannot be excluded. These include personality traits such as introversion or low sensation seeking, which may predict less physical activity and increased risk of PD,[12, 13] although these associations tend to be weak and seem unlikely to fully explain the results of this as well as previous investigations.

Previously, the protective potential of physical activity against PD risk was investigated in three prospective cohort studies, two restricted to men and one including both genders. In a nested case-control study within the College Alumni Health Study (men), based on 117 cases identified through questionnaires, of which 70% were physician-confirmed, and 20 cases identified through death certificates with no further confirmation, increased walking distance, participation in sports, and total energy expenditure were non-significantly associated with a lower PD incidence or mortality.[3] A similar non-significant reduction in self-reported PD risk or mortality with increasing physical activity was found in a recent follow-up of a subset of participants in the same cohort.[2] The third study was based on 387 physician-confirmed or medical record-confirmed cases from the combined HPFS (men) and NHS (women) cohorts, and was similar to the present study in measurement of physical activity and confirmation of PD cases.[1] Among men in the HPFS, vigorous physical activity at baseline was inversely associated with PD risk, and so was strenuous physical activity in high school, in college, and at ages 30–40. Our results for baseline physical activity in men were similar to those in the HPFS, but we did not see an inverse association between physical activity at age 40 and PD risk in the present study. Women in the NHS had no decreased risk of PD regardless of their physical activity levels, except a nonsignificantly decreased risk associated with high levels of strenuous physical activity in early adulthood. The reasons for the gender difference observed between the men in the HPFS and the women in the NHS were not clear. Although a formal synthesis of the results of all the studies is difficult because of differences in methods, the epidemiological studies taken together provide reasonably consistent support for the hypothesis that physical activity is associated with modestly decreased PD risk among men, and possibly among women.

Our study has notable strengths, including prospective data collection, inclusion of both men and women, a large number of confirmed incident PD cases, and thorough data about variables that might have confounded the association between physical activity and PD. Our study also has some limitations. First, physical activity was measured solely by self-report, through a limited number of survey questions, and some level of misclassification was thus inevitable. Because of the longitudinal design of the study, this misclassification was most likely non-differential with respect to disease risk and thus likely attenuated the true relative risks. Physical activity has previously been shown to be inversely related to breast cancer and colon cancer in this cohort, indirectly supporting the validity of the exposure measurement.[8, 9] Second, we may have had some diagnostic error by relying on neurological medical records and reports from treating physicians rather than in-person examinations of study participants. However, the clinical diagnosis of PD by neurologists[10] and especially by movement disorders specialists[11] has been found to be accurate, so bias from misdiagnosis is likely to be modest.

A causal link between physical activity and PD risk is supported by some experimental data, though the potential mechanisms have not been fully elucidated. Experiments in rodent models of PD have shown sparing of neurochemical and behavioral deficits through forced use of the contralateral (impaired) forelimb for seven days prior to administration of the neurotoxin 6-hydroxydopamine.[14] These animals not only had attenuation of striatal dopamine loss, but also an exercise-induced increase in striatal glial cell-line derived neurotrophic factor (GDNF), suggesting that GDNF or another neural growth factor was involved in neuroprotection. Another plausible mechanism is provided by the effects of physical activity on plasma urate, an endogenous antioxidant which may be related to PD risk.[15] Experimental studies in healthy men have shown that exercise increases plasma urate levels.[16] High plasma urate is associated with reduced PD risk in well-designed prospective epidemiological cohorts,[17, 18, 19] and predicts slower clinical progression in PD patients.[20, 21] Whether physical activity influences PD risk through increasing plasma urate, increasing neural growth factors, or through some other means remains to be determined.

In summary, the results of our study favor a role for physical activity in the prevention of PD, and other prospective epidemiological studies on this topic have been reasonably consistent. PD is likely to have a multifactorial etiology, whereby environmental and genetic susceptibility factors interact to create the conditions leading to the onset of the disease.[22] Under such a paradigm, individual factors may have only modest associations with PD risk. Recreational physical activity may be such a factor. Improved physical activity measurement in large research studies, additional data for women, and elucidation of biochemical pathways will advance our understanding of the importance of physical activity for neuroprotection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by grant NS048517 from the National Institute of Neurological Disorders and Stroke (A.A.) and (in part) by the Intramural Research Program of the NIH, the National Institute of Environmental Health Sciences (H.C.). We are grateful to the participants in the Cancer Prevention Study II Nutrition Cohort. We thank Eilis O'Reilly for technical assistance in data analysis.

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Table

Multivariate Adjusted Relative Risks (95% CI) of Parkinson's Disease According to Categories of Baseline Recreational Physical Activity in the Cancer Prevention Study II Nutrition Cohort (1992–2001), Primary Analyses[a]

	Men and women		Men		Women	
	Cases/PY	RR (95%CI)	Cases/PY	RR (95%CI)	Cases/PY	RR (95%CI)
Total activity (light and moderate to vigorous activity combined)						
Zero activity	38/117,685	1.0 (ref)	28/59,765	1.0 (ref)	10/57,920	1.0 (ref)
3.5 MET-h/wk (men and women)	112/333,679	1.1 (0.7, 1.6)	72/136,152	1.0 (0.7, 1.6)	40/197,527	1.2 (0.6, 2.5)
4.0–13.5 MET-h/wk (men); 4.0–8.5 MET-h/wk (women)	77/195,447	1.2 (0.6, 2.2)	45/92,955	0.9 (0.6, 1.5)	32/102,492	1.8 (0.8, 3.7)
14.0–22.5 MET-h/wk (men); 9.0–18.0 MET-h/wk (women)	104/284,101	1.0 (0.7, 1.5)	67/124,020	0.9 (0.6, 1.5)	37/160,081	1.3 (0.6, 2.6)
≥ 23 MET-h/wk (men); = 18.5 MET-h/wk (women)	78/264,171	0.8 (0.6, 1.2)	52/119,218	0.8 (0.5, 1.2)	26/144,954	1.0 (0.5, 2.2)
P for trend		0.07		0.09		0.46
Moderate to vigorous activity (with or without light activity)						
Zero activity or light activity only	254/723,015	1.0 (ref)	170/324,256	1.0 (ref)	84/398,759	1.0 (ref)
4 MET-h/wk (men and women)	54/142,213	1.1 (0.7, 1.6)	30/61,104	0.9 (0.6, 1.3)	24/81,108	1.3 (0.8, 2.1)
4.5–6.0 MET-h/wk (men); 4.5 MET-h/wk (women)	37/85,572	1.2 (0.9, 1.7)	23/32,091	1.2 (0.8, 1.9)	14/53,481	1.2 (0.7, 2.1)
6.5–15.5 MET-h/wk (men); 5.0–11.0 MET-h/wk (women)	33/120,826	0.8 (0.3, 1.8)	17/59,052	0.5 (0.3, 0.8)	16/61,774	1.2 (0.7, 2.0)
≥ 16 MET-h/wk (men); = 11.5 MET-h/wk (women)	31/123,458	0.6 (0.4, 1.0)	24/55,607	0.7 (0.5, 1.1)	7/67,851	0.4 (0.2, 1.0)
P for trend		0.02		0.08		0.07

[a]Results for men and women were pooled using random effects models. Light activity included walking and dancing; moderate to vigorous activity included jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, and aerobics/calisthenics. Models were adjusted for age, pack years of smoking, years since quitting smoking, alcohol intake, caffeinated coffee intake, total caloric intake, dairy intake, body mass index, pesticide exposure, ibuprofen use, and level of education.

PY = person years; RR = relative risk; CI = confidence interval; MET = metabolic equivalent task.