Erectile Function and Risk of Parkinson’s Disease

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Erectile dysfunction is common among individuals with Parkinson’s disease, but it is unknown whether it precedes the onset of the classic features of Parkinson’s disease. To address this question, the authors examined whether erectile dysfunction was associated with Parkinson’s disease risk in the Health Professionals Follow-up Study. Analyses included 32,616 men free of Parkinson’s disease at baseline in 1986 who in 2000 completed a retrospective questionnaire with questions on erectile dysfunction in different time periods. Relative risks were computed using Cox proportional hazards models adjusting for age, smoking, caffeine intake, history of diabetes, and other covariates. Among men who reported their erectile function before 1986, 200 were diagnosed with Parkinson’s disease during 1986–2002. Men with erectile dysfunction before 1986 were 3.8 times more likely to develop Parkinson’s disease during the follow-up than were those with very good erectile function (relative risk = 3.8, 95% confidence interval: 2.4, 6.0; p < 0.0001). Multivariate-adjusted relative risks of Parkinson’s disease were 2.7, 3.7, and 4.0 (95% confidence interval: 1.4, 11.1; p = 0.008) for participants with first onset of erectile dysfunction (before 1986) at 60 or more, 50–59, and less than 50 years of age, respectively, relative to those without erectile dysfunction. In conclusion, in this retrospective analysis in a large cohort of men, the authors observed that erectile dysfunction was associated with a higher risk of developing Parkinson’s disease.

Impotence; Parkinson disease

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; RR, relative risk.

The autonomic nervous system is often affected in Parkinson’s disease (1–3), and erectile function, which is controlled by the autonomic system, is commonly compromised (1, 4–7). An important question is whether erectile dysfunction precedes the onset of motor symptoms of Parkinson’s disease. If so, examination of erectile function could eventually contribute to the identification of men who are at high risk or in a preclinical stage of Parkinson’s disease. An increased risk of Parkinson’s disease has been associated with constipation, also a common symptom of autonomic dysfunction (1, 8, 9); however, to our knowledge, there have been no studies to examine if erectile dysfunction precedes onset of Parkinson’s disease. Moreover, erectile dysfunction and Parkinson’s disease share several common mechanisms, such as status of dopamine and testosterone (6, 10, 11). Dopamine has a fundamental role in the mediation of erectile function (11), whereas testosterone deficiency has been shown to be more common among Parkinson’s disease patients than age-matched controls (12). We, therefore, examined whether baseline erectile dysfunction was associated...
with Parkinson’s disease risk during 16 years of follow-up in the Health Professionals Follow-up Study (HPFS), a large ongoing cohort of US men.

MATERIALS AND METHODS

The HPFS was established in 1986, when 51,529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 years completed a mailed questionnaire about their medical history and lifestyle. Follow-up questionnaires have been mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases. Dietary intake data were collected since 1986 and updated every 4 years.

On the 2000 questionnaire, we asked HPFS participants who were still alive and actively participating in the study (n = 43,235) to rate their ability to have and maintain an erection sufficient for intercourse before 1986, 1986–1989, 1990–1994, 1995–2000, and during the past 3 months. There were five possible responses: very poor, poor, fair, good, and very good. Reports of poor or very poor erectile function were considered erectile dysfunction, as we did previously (13, 14). The questionnaires were mailed up to four times to nonrespondents and yielded 34,282 responses. For persistent nonresponders, we mailed a short version of the questionnaire that did not include questions on erectile function. The questions on erectile function were completed by 32,663 participants. Subjects with Parkinson’s disease have response rates similar to those without Parkinson’s disease (80 vs. 82.7 percent). We excluded men with a diagnosis of Parkinson’s disease before enrollment in the cohort from this analysis. Overall, 47 men were excluded, and the remaining 32,616 men were included in the current analyses. We used reported erectile function before 1986 as the exposure of interest in the primary analyses.

Information on potential confounders, including age, weight, height, smoking status, physical activity, use of medicines, and history of diabetes, hypertension, and stroke, was collected via biennial questionnaires through the follow-up, as previously described. Body mass index was calculated as weight (kg)/height (m)². Dietary intakes were assessed with a semiquantitative food frequency questionnaire validated for use in this population (15).

Ascertainment of Parkinson’s disease

As previously described (16), we identified new Parkinson’s disease cases by biennial self-reported questionnaires. We then asked the treating neurologists to complete a questionnaire to confirm the diagnosis of Parkinson’s disease or to send a copy of the medical records. A case was confirmed if a diagnosis of Parkinson’s disease was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of Parkinson’s disease made by a neurologist or evidence 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 percent of the cases, by review of the medical records in 7.4 percent, and by the treating internist without further support in the remaining 11.3 percent. We also requested the death certificates of the deceased study participants and identified Parkinson’s disease diagnoses that were not reported in the regular follow-up (<2 percent). If Parkinson’s disease was listed as a cause of death on the death certificate, we requested permission from the family to contact the treating neurologist or physician and followed the same procedure as for the nonfatal cases.

Statistical analysis

We computed the person-time of follow-up for each participant from the return date of the baseline questionnaire in 1986 to the date of the occurrence of the first symptoms of Parkinson’s disease, the date of death, or the end of follow-up (January 31, 2002), whichever came first. In the primary analysis, we examined the relation between erectile function before 1986 and Parkinson’s disease risk from 1986 to 2002. Baseline erectile function was divided into three categories (very good, good or fair, and poor or very poor). Multivariate-adjusted relative risks of Parkinson’s disease were derived from Cox proportional hazards models controlling for age (in months), smoking status (as above), body mass index (<23, 23–24.9, 25–26.9, 27–29.9, or ≥30 kg/m²), physical activity (quintiles), use of nonaspirin nonsteroidal antiinflammatory drug (yes/no), caffeine (quintiles), and presence of cancer, stroke, hypertension, myocardial infarction, or diabetes in 1986 (each of them, yes/no). All covariates utilized the values from the baseline questionnaire in 1986. In secondary analyses, we also took into account erectile function after 1986 and examined the association between erectile function at different times during the follow-up and the risk of Parkinson’s disease in the following 4-year period. For example, we related incidence of Parkinson’s disease between 1990 and 1994 to reported erectile function in 1986–1989 and related incidence of Parkinson’s disease between 1995 and 2000 to erectile function in 1990–1994.

We also examined potential interactions between erectile function and baseline age (<60 vs. ≥60 years), smoking status (never vs. ever), body mass index (<25 vs. ≥25 kg/m²), and caffeine intake (0–149 vs. ≥150 mg/day, based on median intake) or reported diabetes at any time during the follow-up (yes/no), by adding multiplicative terms in the Cox models. To examine the temporal relation between erectile dysfunction and Parkinson’s disease, we conducted 4-year and 8-year lag analyses by excluding the first 4 years and 8 years, separately, of follow-up. All statistical analyses were performed using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). All statistical tests were two tailed.

RESULTS

During 16 years’ follow-up, we documented 200 incident Parkinson’s disease cases among men who provided
information on their erectile function in the 2000 survey. Participants with erectile dysfunction defined as having poor or very poor erectile function prior to baseline were older and more likely to smoke, had a higher body mass index, had a higher prevalence of major chronic disease (cancer, stroke, hypertension, myocardial infarction, or diabetes), and consumed larger amounts of caffeine than did those who reported very good function (table 1).

As expected, the prevalence of erectile dysfunction increased with age (figure 1). However, men with Parkinson’s disease had a higher prevalence of erectile dysfunction relative to those without Parkinson’s disease in each age group. In 2000, 68.0 percent of Parkinson’s disease patients reported erectile dysfunction during the past 3 months, relative to 32.0 percent of participants without Parkinson’s disease \( (p < 0.0001) \). After adjusting for age, smoking status, and body mass index. Among participants without diabetes, the prevalences of erectile dysfunction were 68.8 percent and 31.2 percent for men with and without Parkinson’s disease, respectively, and for participants with diabetes, 61.9 percent and 38.1 percent, respectively.

Subjects who reported erectile dysfunction before 1986 were 3.8 times more likely to develop Parkinson’s disease, relative to those who reported very good function (multivariate relative risk \( RR = 3.8, 95 \text{ percent confidence interval (CI): 2.4, 6.0; } p < 0.0001 \) ) (figure 2A). This association was stronger among men who reported erectile dysfunction at younger ages: The multivariate relative risks of Parkinson’s disease were 2.7, 3.7, and 4.0 (95 percent CI: 1.4, 11.1; \( p = 0.008 \) ) for men with first onset of erectile dysfunction (before 1986) at 60 or more, 50–59, and less than 50 years of age, respectively, relative to those without erectile dysfunction (figure 2B). To test the robustness of the association, we conducted several sensitivity analyses that generated similarly significant results. The multivariate relative risk of Parkinson’s disease comparing men with erectile dysfunction with men with very good function was 3.9 (95 percent CI: 2.5, 6.2; \( p < 0.0001 \) ) after excluding men with prostate cancer at baseline and 4.0 (95 percent CI: 2.5, 6.5; \( p < 0.0001 \) ) after excluding men with cancer and stroke at baseline. The significant associations remained in the lag analyses that excluded the first several years of follow-up: The corresponding relative risks were 3.3 (95 percent CI: 2.0, 5.5; \( p < 0.0001 \) ) in the 4-year lag analyses and 3.2 (95 percent CI: 1.8, 5.8; \( p < 0.0001 \) ) in the 8-year lag analyses. A significant association with Parkinson’s disease risk was also observed for erectile function after 1986; adjusted relative risks were 1.3 and 2.9 (95 percent CI: 1.8, 4.7; \( p < 0.0001 \) ) for participants with good/fair and poor/very poor erectile function, respectively, in a comparison with those with very good function.

We further explored possible interactions of erectile function with age, body mass index, cigarette smoking, caffeine intake, and the presence of diabetes during follow-up (yes/no). None of these interactions was significant. The association between erectile function and risk of Parkinson’s disease was similar in men with diabetes (adjusted \( RR = 3.7 \) ) and those without (adjusted \( RR = 4.2 \) ). An association between erectile function and Parkinson’s disease risk also remained evident in subgroup analyses according to age, smoking status, body mass index, and caffeine intake at baseline (data not shown).

### TABLE 1. Baseline characteristics in 1986 according to reported erectile function before 1986 in the Health Professionals Follow-up Study*

<table>
<thead>
<tr>
<th>Reported erectile function before 1986</th>
<th>Very good</th>
<th>Good or fair</th>
<th>Poor or very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>23,045</td>
<td>8,504</td>
<td>1,067</td>
</tr>
<tr>
<td>No. of Parkinson’s disease cases</td>
<td>95</td>
<td>74</td>
<td>31</td>
</tr>
<tr>
<td>Parkinson’s disease incidence (rate/100,000 person-years)</td>
<td>27</td>
<td>56</td>
<td>189</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.0</td>
<td>57.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>7.6</td>
<td>8.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Past smokers (%)</td>
<td>41.0</td>
<td>41.4</td>
<td>41.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3</td>
<td>25.5</td>
<td>26.3</td>
</tr>
<tr>
<td>Physical activity (metabolic equivalents/week)</td>
<td>22.8</td>
<td>19.7</td>
<td>21.2</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>11.5</td>
<td>11.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Caffeine intake (mg/day)</td>
<td>228</td>
<td>241</td>
<td>243</td>
</tr>
<tr>
<td>Presence of cancer in or prior to 1986 (%)</td>
<td>2.7</td>
<td>2.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Presence of stroke in or prior to 1986 (%)</td>
<td>0.3</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Presence of hypertension in or prior to 1986 (%)</td>
<td>17.7</td>
<td>20.9</td>
<td>28.0</td>
</tr>
<tr>
<td>Presence of diabetes in or prior to 1986 (%)</td>
<td>1.4</td>
<td>2.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Presence of myocardial infarction in or prior to 1986 (%)</td>
<td>2.3</td>
<td>3.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Use of nonaspirin nonsteroidal antiinflammatory drug (%)</td>
<td>9.5</td>
<td>9.5</td>
<td>9.2</td>
</tr>
</tbody>
</table>

* Values were standardized to the age distribution of the overall cohort.
DISCUSSION

In this large-scale cohort with 32,616 US men, we observed that erectile dysfunction was prevalent among Parkinson’s disease patients. Two thirds of them reported poor or very poor erectile function relative to 32 percent of participants without Parkinson’s disease, a result consistent with previous studies (1, 5, 6). Moreover, erectile function before 1986 appeared to be strongly associated with Parkinson’s disease risk. Participants who reported erectile dysfunction had a fourfold higher risk of developing Parkinson’s disease over 16 years of follow-up, relative to those who reported very good function. This association was still strong and significant after exclusion of Parkinson’s disease cases with onset during the first 8 years of follow-up.

Our results that erectile dysfunction antedates the Parkinson’s disease-associated motor dysfunctions by many years are in line with the pathologic findings of Braak et al. (9), which suggests that many nonmotor symptoms, such as olfaction, and autonomic dysfunction could be early signs of preclinical stages of Parkinson’s disease development (9). Consistently, the prospective Honolulu-Asia Aging Study showed that constipation (defined as less than one bowel movement per day) was associated with a 170 percent increased risk of Parkinson’s disease in 6,780 Japanese men, after 24 years’ follow-up (8). Interestingly, both constipation and erectile dysfunction are manifestations of parasympathetic cholinergic failure (2). Dopamine status could be another potential mechanism underlying the association between erectile function and Parkinson’s disease risk. Central regulation of erectile function is dependent on dopaminergic stimulation (6, 17). This has been supported by the observations that apomorphine, a dopaminergic agonist, can induce erections in Parkinson’s disease patients (6, 17). Testosterone levels, which are important for erectile function (10), could also partially explain the observed association between erectile dysfunction and Parkinson’s disease. Testosterone deficiency has been reported to be more common in Parkinson’s disease patients relative to age-matched controls (12), and several studies reported beneficial effects of testosterone administration on motor and nonmotor symptoms among Parkinson’s disease patients (18, 19). Furthermore, because erectile function is regulated by a complex set of systems, any change due to a clinically unrecognized stage of Parkinson’s disease, such as changes in the nervous system, hormones, or interpersonal relations, could affect erectile function and, therefore, result in the observation of erectile dysfunction preceding Parkinson’s disease. The complicated relations between erectile dysfunction and Parkinson’s disease thus remain to be elucidated.

Our study has several limitations. Because we first collected erectile function information only in 2000, this
analysis, unlike previous investigations on Parkinson’s disease in this cohort, was largely retrospective. Thus, we were unable to obtain baseline erectile function in 1986 for participants who died, were lost to follow-up during 1986–2000, or did not answer this particular question on the 2000 questionnaire. However, participants without 1986 erectile function data had a similar Parkinson’s disease risk (RR = 1.1; \( p = 0.4 \)) as did the participants included in our analyses. Recall bias could be a concern if men with Parkinson’s disease were more or less likely than others to recall or report their experience of erectile dysfunction and to place it correctly in time. However, the magnitude of the observed association was rather large and might not be totally explained by recall bias. Moreover, a strong association between erectile dysfunction and Parkinson’s disease does not necessarily mean that erectile dysfunction is a good predictor of Parkinson’s disease at the individual level (20, 21). Nonetheless, information on erectile dysfunction, in addition to information on other premorbid characteristics such as loss of olfaction or constipation, could contribute to the identification of groups of individuals with an increased risk of Parkinson’s disease. These groups could be targeted in investigations of diagnostic biomarkers or preventive interventions.

In conclusion, in this retrospective analysis of a large cohort of men, we observed that erectile dysfunction was associated with a higher future risk of developing Parkinson’s disease. Magnitudes of the association were inversely associated with age at the first onset of erectile dysfunction. This finding adds new evidence in support of the hypothesis that the autonomous nervous system may have been impaired years before Parkinson’s disease is clinically recognizable.

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None of the sponsors participated in the design of the study or in the collection, analysis, or interpretation of the data.

Conflict of interest: Dr. Dale B. Glasser is employed by Pfizer, Inc., and holds stock in Pfizer, Inc.

REFERENCES