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Sex-Dependent Improvement in Survival of Parkinson's Disease Patients

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ABSTRACT: Background: Advances in the treatment of Parkinson's disease (PD) and changes in general life expectancy may have improved survival in patients with PD.

Objective: The objective of this study was to investigate recent trends in PD mortality.

Methods: In total, 1521 patients with PD in local and national registries were followed for 11 years (2006–2016) from diagnosis until exit date or death, and the causes of death were recorded.

Results: The survival of men with PD improved during the follow-up period, but no change was observed in women (2-year postdiagnosis survival in men, 79.0%–86.3%, $P = 0.03$; 2-year postdiagnosis survival in women, 82.8%–87.5%, $P = 0.42$). Pneumonia was the most common immediate cause of death.

Discussion: The survival of men with PD has improved in Finland without a similar change in women. Because changes in treatment likely affect both sexes similarly, the results may reflect the decreasing sex gap in life expectancy. This phenomenon will likely increase the already high male-to-female prevalence ratio of PD.

Parkinson's disease (PD) is associated with increased mortality, as, on average, survival is reduced by approximately 5% every year in followed cohorts.¹ Although studies have demonstrated the effectiveness of monoamine oxidase-B inhibitors,^{2–6} dopamine agonists,^{7–11} and levodopa^{12,13} in the earlier stages of PD, the effects of antiparkinsonian medications on PD mortality remain speculative. In recent years, in line with new evidence, the traditional view of early pharmacotherapy has started to shift from delayed levodopa at advanced stages of PD to earlier initiation of low-dose therapy for improved quality of life.^{14–16} Otherwise, the primary pharmacotherapy for early and moderate PD has remained mostly unaltered for the past two decades in developed countries,^{17–19} and there are no sex-specific recommendations for drug therapy in PD.²⁰

The greatest improvements in PD treatment have recently been documented in patients with advanced PD. Device-aided therapies have induced treatment effects that appear to surpass those of optimal oral drug therapy in advanced PD.^{21–25} However,

although deep brain stimulation and pump therapies induce clear effects on quality of life in advanced PD, there is a similar lack of current evidence for increased survival.^{21,23–26} Nevertheless, there are potentially highly relevant changes in treatment that could affect mortality, namely, improved rehabilitation, fall prevention, and changes in the end-of-life care for patients with PD.^{27–31}

It is hypothesized that changes in the care of PD have increased the life expectancy (LE) of patients with PD. Nevertheless, as a late-life neurodegenerative disease, PD epidemiology is also affected by general factors that increase or decrease LE. Moreover, the sex gap in LE has been reported to narrow.³² Here, we investigated possible changes in the mortality of a large hospital-based cohort of Finnish patients with PD in three different time points with respect to time of PD diagnosis by following a total of 1521 patients with PD in local and national registries for 11 years and taking into account the effects of device-aided therapies, causes of death, and general changes in LE.

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Keywords: Parkinson's disease, survival, mortality, gender, sex.

Relevant disclosures and conflicts of interest are listed at the end of this article.

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TABLE 1 Demographic characteristics of the patients and changes in the overall survival according to the year of PD diagnosis

Year of Diagnosis	Diagnoses, M/W, n (%)	Age at Diagnosis, M/W, (y)	Deaths, M/W, n	Overall Survival, M/W, % ^a			Hazard Ratio (95% CI, P), M/W
				1 Year After Diagnosis	2 Years After Diagnosis	4 Years After Diagnosis	
2006–2008	271/256 (51.4/48.6)	72.2/74.3	191/154	86.0/89.8	79.0/82.8	62.0/69.1	–
2009–2011	261/225 (53.7/46.3)	71.7/74.2	122/96	90.4/94.2	82.8/88.4	67.8/74.7	0.80 (0.63–1.01, 0.057)/ 0.92 (0.70–1.20, 0.534)
2012–2014	292/216 (57.5/42.5)	71.0/73.8	75/47	91.1/93.1	86.3/87.5	71.5/77.3	0.71 (0.53–0.95, 0.019)/ 0.79 (0.56–1.12, 0.191)
Total	824/697 (54.2/45.8)	71.6/74.1	388/297				–

^aP value for Kaplan-Meier analysis: M, $P = 0.03$; W, $P = 0.42$.

M, men; W, women; CI, confidence interval.

Methods

The Turku Clinical Research Center (<http://www.turkucrc.fi/en>) maintains the Turku University Hospital database, which stores all electronic health records generated at the hospital for medical research. Health records have been in electronic format from January 1, 2004, onward, enabling annual longitudinal analyses, and they include demographics, clinical diagnoses and procedures, inpatient periods and outpatient visits, pathology diagnoses and reports, imaging reports, chemotherapy and radiation treatments, inpatient medications and outpatient prescriptions, laboratory measurements, and clinical narratives. At present, the database contains detailed clinical data of approximately 0.5 million patients who have visited Turku University Hospital or regional hospitals. The data are pseudonymized, protecting the identity of the patients while making it possible to link data elements to individual patients.

The study population consisted of patients with PD diagnosed between 2006 and 2014 at Turku University Hospital in southwestern Finland. The hospital district has a population base of approximately 470,000 people. Our study cohort included only patients from the university hospital database, and the great majority of diagnoses were based on outpatient visits. We employed a methodological approach that involved the investigations of complete, digital, detailed individual health records during a period of 11 years. Patients with PD were identified

from the digital database using the *International Classification of Diseases 10th Revision* code G20. All diagnoses of PD were based on clinical examination by a certified neurologist using the UK Brain Bank Criteria or Movement Disorder Society clinical diagnostic criteria.³³ The date of diagnosis was defined as the first appearance of the diagnosis code in the patient records. After identifying patients and diagnosis dates, all individual clinical data were collected from the database. Dates and individual causes of death were obtained from the national authority, Statistics Finland (www.stat.fi). The beginning of the follow-up period was January 1, 2006, and the end of the follow-up period was set to December 31, 2016.

To investigate possible longitudinal changes in survival, the cohort was divided into the following three groups based on the year of diagnosis: 2006 to 2008, 2009 to 2011, and 2012 to 2014. Data analysis was separately performed for a sample in which patients with device-aided therapies were excluded. The overall survival (OS) was defined as the percentage of patients who were still alive after their diagnosis at the following time points: 1, 2, and 4 years. Hence, survival was investigated identically for every patient with PD at 1 and 2 years from the diagnosis. Therefore, our main result of the OS at 2 years after diagnosis has been evaluated similarly and is valid for all patients. The 4-year time point was evaluated similarly for the 2006 to 2008 and 2009 to 2011 groups. However, because the end of our follow-up was set at December 31, 2016, the result of the

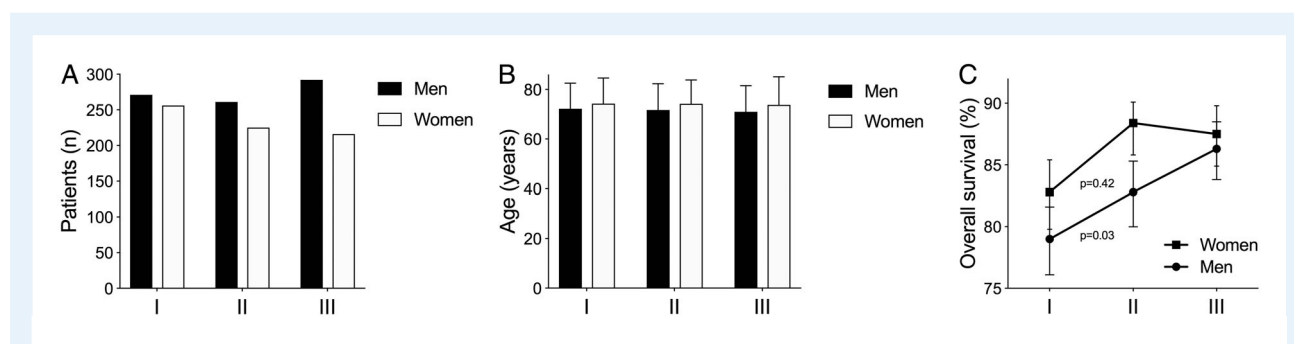


FIG. 1. Demographic characteristics of the sample according to the year of Parkinson's disease diagnosis: (A) number of new diagnosis, (B) age at diagnosis, and (C) overall survival 2 years after diagnosis according to follow-up period. Note the increased overall survival in men but not in women in C. I = diagnosis years 2006 to 2008, II = diagnosis years 2009 to 2011, III = diagnosis years 2012 to 2014.

TABLE 2 The 3 most common immediate causes of death in the studied cohorts (I, II, III) in patients with PD according to sex and year of diagnosis

Year of Diagnosis	Gender	Cohort			PD as a Contributing Factor, n/%
		I, n/%	II, n/%	III, n/%	
2006–2008	M	Pneumonia (72/37.7)	HF (7/3.7)	MI (3/1.6)	77/40.3
	W	Pneumonia (45/29.2)	HF (5/3.2)	MI (5/3.2)	64/41.6
2009–2011	M	Pneumonia (49/40.2)	MI (5/4.1)	CA (2/1.6)	41/33.6
	W	Pneumonia (22/22.9)	MI (3/3.1)	HF (2/2.1)	34/35.4
2012–2014	M	Pneumonia (27/36.0)	HF (4/5.3)	MI (2/2.7)	23/30.7
	W	Pneumonia (10/21.3)	MI (3/6.4)	HF (2/4.3)	16/34.0
Total	M	Pneumonia (148/38.2)	HF (12/3.1)	MI (10/2.6)	141/36.3
	W	Pneumonia (77/25.9)	MI (11/3.7)	HF (9/3.0)	114/38.4

The immediate cause of death was not reported for 43.6% of men and 57.2% of women.

PD, Parkinson's disease; M, men; W, women; HF, heart failure; MI, myocardial infarction; CA, cardiac arrest.

OS 4 years after diagnosis in patients with PD diagnosed between 2012 and 2014 was estimated using the Kaplan–Meier analysis. To investigate possible differences in the correctness of PD diagnoses between men and women, changed or removed diagnoses were investigated within a 2-year timeline in 2011 (midpoint of the follow-up period). We also analyzed potential changes in antiparkinsonian medication according to sex.

The study was approved by Turku Clinical Research Center (TT263/2017, diary number TK-53-652-18). Because the study did not involve patient contacts, approval of the ethics committee was not required.

Continuous and categorical variables were compared between groups using analysis of variance and chi-square tests, respectively. Kaplan–Meier analysis was used to analyze changes in the OS. Log-rank tests were used to calculate the *P* values between survival curves. The level of statistical significance was set to *P* < 0.05. All statistical analyses were performed with IBM SPSS Statistics for Windows (version 25.0, 2017, IBM Corp., Armonk, NY).

Results

We identified 1521 patients with PD (54.2% men; Table 1, Fig. 1). The number of new diagnoses of PD per year remained stable during the study period (men, 261–292 diagnoses per three years, *P* = 0.14; women, 216–256 diagnoses per three years, *P* = 0.14). Men were diagnosed at a younger age than women (71.6 years [SD, 10.5 years] vs. 74.1 years, [SD, 10.4 years]; *P* < 0.01), but the age difference and mean age at diagnosis remained stable (men, *P* = 0.41; women, *P* = 0.84). In 2011, at the midpoint of the follow-up period, 55 men and 54 women were diagnosed with PD. Two years later, the diagnoses remained unaltered for 42 of men (76.4%) and 42 of women (77.8%). There were no significant differences in the diagnostic inaccuracy between men and women (men, 23.6%; women, 22.2%; *P* = 0.86; Supplementary Table S1). During the 11-year study period, 685 patients died (47.1% of men and 42.6% of women). The OS of male patients with PD increased during the follow-up period (*P* = 0.03), but no change was observed in women (*P* = 0.42; Table 1, Fig. 1). The hazard ratio for men in

the last follow-up period was 0.71 (95% confidence interval, 0.53–0.95; *P* = 0.02), indicating better survival for men if the diagnosis was made later in the follow-up period. The results remained the same when patients receiving device-aided therapies (*n* = 29) were excluded from the analysis. The number of patients with PD using levodopa and dopamine agonists remained stable during the study period in both sexes (levodopa: men, 55.2%–60.6% per three years, *P* = 0.39 and women, 54.2%–60.2% per three years, *P* = 0.41; dopamine agonists: men, 40.6%–43.8% per three years, *P* = 0.72 and women, 38.2%–41.8% per three years, *P* = 0.24; Supplementary Table S2).

Pneumonia was the most common immediate cause of death in all 3 time periods in both men and women (38.2% of deaths in men and 25.9% of deaths in women; Table 2). The second and third most common causes of death were heart failure and myocardial infarction, respectively. There were no marked changes in the causes of death during the study period. PD was reported as a contributing factor to death in 36.3% of men and 38.4% of women, and the percentage did not change significantly during the follow-up period (men, 40.3% vs. 33.6% vs. 30.7%, *P* = 0.25; women, 41.6% vs. 35.4% vs. 34.0%, *P* = 0.50; Table 2).

Discussion

The results demonstrate that the mortality of male Finnish patients with PD has decreased during a period of 11 years. No significant changes in the mortality of female patients with PD were observed. In Finland, the diagnostic criteria and treatment lines of PD are regionally homogeneous and are based on national current care guidelines. Therefore, the result could reflect greater improvements in male survival compared with female survival at the population level, and the same sex differences can likely be seen in other regions with aging PD populations and comparable health care systems.

Competing causes of death refers to an epidemiological fact that if a patient is cured and will not die from one disease, he or she is eligible to have another fatal disease. The most important reason for the demonstrated change in the LE of male patients with PD could be caused by population-level changes in

morbidity and mortality. Between 2006 and 2016, the general LE of Finnish newborns increased by 1.3 years in girls and 2.6 years in boys.³⁴ Similarly, in 73-year-old individuals in the general population (mean age of the present PD population), the LE increased almost twice as much in men compared with women (1.1 vs. 0.6 years).³² The present results may thus at least partially be related to the decreasing sex differences in survival. There are several reasons for the increased LE in men in Finland, but successful actions taken for the prevention and control of noncommunicable diseases are probably contributing. Cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes are the most important causes of death worldwide and have affected more men than women.³⁵ In Finland, the most important cause of death has long been ischemic heart disease, and age-standardized mortality for circulatory diseases has declined, especially in men.³⁶

Studies have reported that there are no differences in the type of dopaminergic medication prescribed to women and men, but men are often medicated with higher doses of levodopa both orally and via infusion.²⁰ This is most likely attributed to the higher average body mass of men.²⁰ However, the differences may not be solely explained by differences in body weight, as there are sex differences in levodopa bioavailability, irrespective of body weight.^{37,38} In addition, men are more often treated with deep brain stimulation than women in PD, although women more commonly suffer from motor fluctuations and dyskinesia.^{20,39} Diagnostic conventions and pharmacotherapy for PD remained essentially the same in Finland during the study period, as did the proportion of male and female patients with PD using levodopa and dopamine agonists in our cohort. We do not suspect that sex differences in therapy were a major contributing factor in the results. Moreover, the results remained the same when the small number of patients treated with device-aided therapies were excluded from the analysis. We did observe a slight difference in the ages at diagnosis between men and women (mean difference of 2.5 years; men were diagnosed earlier). It has been suggested that the phenotype of PD in women may be more benign and that symptoms may begin later for women than in men, which could explain this difference.²⁰ It should be noted that nonpharmacological therapies, including physiotherapy, speech therapy, and occupational therapy, are given mainly in local health care centers in Finland. These data were not available for us, and this can be considered as a limitation of our study because the convention and intensity of these therapies might have changed during the follow-up period.

In summary, the present study shows that there is disparity in mortality between male and female patients with PD, which will probably lead to an increasing male-to-female ratio in PD prevalence.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,

C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

T.K.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

S.K.: 1C, 2A, 2B, 2C, 3B

J.S.: 1C, 2C, 3B

H.S-M.: 1B, 1C, 2C, 3B

O.C.: 1B, 1C, 2C, 3B

V.K.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. The study was approved by Turku Clinical Research Center (TT263/2017, diary number TK-53-652-18). Informed consent was not required. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Supplementary Table S1. The percentage of patients with unchanged PD diagnoses over a 2-year follow-up period (2011–2013) according to sex.

Supplementary Table S2. The number and relative proportion of patients with PD using levodopa and dopamine agonists according to sex and year of diagnosis.