RESEARCH ARTICLE

The Impact of Sex-Specific Survival on the Incidence of Dementia in Parkinson's Disease

Anne Fink, PhD,[1*] Richard Dodel, MD, PhD,[2] Daniela Georges, PhD,[3] and Gabriele Doblhammer, PhD[1,3]

[1]German Center for Neurodegenerative Diseases, Rostock, Germany
[2]Chair of Geriatric Medicine and Center for Translational Neuro- and Behavioural Sciences, University Duisburg-Essen, Essen, Germany
[3]Institute for Sociology and Demography, University of Rostock, Rostock, Germany

ABSTRACT: Objective: The aim of our study is to analyze sex-specific patterns of Parkinson's disease dementia (PDD) incidence. We are investigating the extent to which sex differences in survival after initial Parkinson's disease (PD) diagnosis influence differences in PDD risk among PD patients.
Methods: We used a random sample of German longitudinal health claims data of persons ages 50+ (2004–2019; n = 250,000) and identified new PD cases ages 65+ who were followed-up for a PDD diagnosis or death between 2006 and 2017. We performed Cox and competing-risk regression models, with death as competing event, to calculate PDD hazard ratios (HR) adjusted for age at PD onset, PD severity as measured by the modified Hoehn and Yahr (HY) scale, comorbidities, and medications.
Results: Of 2195 new PD cases, 602 people died before PDD and 750 people developed PDD by the end of 2017. The adjusted risk of PDD differs by sex, with men having a higher PDD risk than women. When accounting for death, men and women do not differ in their PDD risk (HR = 1.02, $P = 0.770$). Sex-specific analyses showed significant age and severity effects in women (age: HR = 1.05, $P < 0.001$; HY 3–5 vs. 0–2.5: HR = 1.46, $P = 0.011$), but not in men.
Conclusion: Older age at first PD diagnosis and higher disease severity increase PDD risk, but this association is attenuated for PD men when controlling for death. This implies that the most frail PD men die rapidly before receiving a dementia diagnosis, whereas women with PD survive at higher rates, regardless of their age at onset and disease severity. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease dementia; competing-risk; epidemiology; sex; Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder at higher ages, and gains increasing relevance in ageing societies.[1-4] Globally, the number of individuals diagnosed with PD was estimated at 6.1 million in 2016.[5] In Germany, the number of prevalent PD patients was estimated at 420,000 in 2015.[6] PD incidence increases with age, but stabilizes in the highest ages, and is higher among males.[6-8]

PD is a chronic progressive disease, and is characterized by varying motor symptoms and non-motor symptoms.[2,5,9,10] Parkinson's disease dementia (PDD) as a non-motor manifestation is present in 13% to 85% of PD patients[6,11-15] and is associated with reduced psychosocial well-being,[16] higher severity of PD,[17] and increased risk of mortality.[18]

The adverse effects of PD and associated health problems will particularly affect women, who are more likely to reach older age because of higher life expectancy.[19,20] In general, the female mortality advantage has been shown to be particularly pronounced after health deterioration,[21] indicating higher survival rates after health crises such as the onset of PD. Findings on

*Correspondence to: Dr. Anne Fink, German Center for Neurodegenerative Diseases, 18057 Rostock, Germany; E-mail: anne.fink@dzne.de

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sex differences in PD mortality are inconsistent.[22-26] Differences in symptom progression, healthcare utilization, and health behaviors, as well as self-selection into clinical trials, have been discussed to explain both the sex differences in PD mortality and the discrepancy in results.[27] Although older age has consistently been found to contribute to higher risk of PDD,[28-30] sex differences have been inconsistently reported, but more often in the form of higher risk and prevalence in men.[28,30-32] Moreover, higher PD severity[29,30,33] as well as comorbidities have been associated with PDD.[34]

For Germany, we identified a limited number of studies on PDD. Most studies are outdated,[30,34,35] report only prevalences,[17,36] or are based on short follow-up periods.[34] All of the studies do not report incidence rates. The results suggest a PDD prevalence of ~30% to 39%.[17,34] The age effect on PDD found in international studies is also evident for Germany.[17] In one region of Germany, a higher prevalence was found in men than in women.[32] To the best of our knowledge, there are no analyses available for Germany on age- and sex-specific transitions of PD patients to PDD, controlling for PD severity, comorbidities, and medications.[37] Furthermore, given the sex differences in mortality, the confounding effect of mortality should be controlled for but it has been neglected in most studies.

The purpose of our study is to analyze the sex patterns of incidence of PDD controlling for important risk factors such as age at PD onset, PD severity, comorbidities, and medications. In addition, we examine the extent to which sex differences in survival after PD diagnosis shape differences in PDD risk. We hypothesize that the comparatively rapid health deterioration of men after the first PD diagnosis leads to increased mortality before the development of PDD, explaining much of the sex difference, as well as the age effect on PDD incidence.

Methods

Data

We used a random sample of longitudinal health claims data of persons ages 50 years or older from the health insurance, the "Allgemeine Ortskrankenkasse" (AOK). In Germany, all citizens are required by law to have health insurance, which is either publicly or privately financed. The AOK is the largest public health insurer in Germany. The sample was drawn in the first quarter of the year 2004 (n = 250,000) and followed up until the end of 2019. The data contain information on sex, age, region of residence, and if applicable, date of death, as well as information on all reimbursed inpatient and outpatient diagnoses coded according to the German modification of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). We had information on all prescriptions filled that were coded according to the Anatomical Therapeutic Chemical (ATC) classification system. All information was available on a quarterly basis.

To create our analysis sample, we first identified all new PD cases. As dementia is rare before age 65, we only looked at persons at ages 65 years or older. We defined 2004 and 2005 as free of any valid PD or dementia diagnosis. Any new PD case without dementia between 2006 and 2015 was defined as a first PD diagnosis. These individuals were followed up for a new dementia diagnosis through the end of 2017. The years 2018 and 2019 were used for validation of PD and dementia diagnoses (Supplementary Fig. S1).

Definition of PD and Dementia

PD was defined by ICD-10 code G20. All persons with at least one diagnosis of progressive supranuclear ophthalmoplegia (G23.1), multisystem atrophy (G23.2–G23.3), dementia with Lewy bodies (G31.82), or corticobasal degeneration (G31.0) were classified as atypical parkinsonism and excluded from our analyses. Dementia was identified by following ICD-10 codes: G30, F00–F03. To overcome the problem of false-positive diagnoses we applied an internal validation strategy. Only inpatient discharge or secondary diagnoses or verified outpatient diagnoses were considered. Diagnoses were defined as valid if they could be confirmed by a second occurrence over time. In the case of dementia, diagnoses were also defined as valid if they appeared simultaneously in the inpatient and outpatient sector or if two types of physicians gave the diagnoses in the same quarter. If a person died in the quarter of the first diagnosis, the diagnosis was considered as valid although there was no confirmative diagnosis. We only considered dementia cases as Parkinson's disease dementia (PDD) if the dementia diagnosis was made at least 1 year after the initial PD diagnosis to exclude probable patients with dementia with Lewy bodies.[38]

Exposure Variables

Our two exposure variables were sex (male, female) and age at the time of first PD diagnosis.

Confounding Variables

Time-varying PD severity was introduced using ICD-10 codes used by physicians and hospitals. We distinguished between the following codes: G20.0, corresponding to stages 0 to 2.5 of the modified Hoehn and Yahr (HY) PD progression scale[39]; G20.1 and G20.2 for HY stages 3 to 5; and G20.9 and G20 codes without a fourth digit, which we referred to as "unknown" classification. We ordered the coded stages from unknown through HY 0–2.5 to HY 3–5. Once a patient was coded with HY 0–2.5, there was no possibility to return to the "unknown" classification. We

included all patients in our analyses regardless of whether the HY stage was explicitly coded or not. We used the following time-varying comorbidity diagnoses associated with dementia: cerebrovascular diseases (I60–I69), hypertension (I10–I15), ischemic heart diseases (I20–I25), hypercholesterolemia (E78.0), atrial fibrillation (I48), type 2 diabetes (E11–E14), depression (F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, and F43.2), psychosis (F20, F22–F25, F28, F29, F30.2, F31.2, and F31.5), and mild cognitive impairment (MCI) (F06.7). The covariates took the value of 1 from the time of initial diagnosis and 0 otherwise. We considered the following medications with a lag-time of four quarters as time-varying covariates: dopa and dopa derivatives (N04BA), dopamine agonists differentiated by ergot derivatives only (N04BC01–N04BC03, N04BC06, and N04BC10), non-ergot derivatives only (N04BC04, N04BC05, and N04BC07–N04BC09; this distinction is necessary as the European Medicines Agency (EMA) has recommended restrictions of the use of ergot derivatives for PD patients following the year 2008) or a combination, entacapone (N04BX02), tertiary amines (N04AA), adamantane derivatives (N04BB), antidepressants (N06A), and antipsychotics (N05A) differentiated by clozapine (N05AH02) or quetiapine (N05AH04) only, any other antipsychotic only or a combination. Clozapine and quetiapine are the only antipsychotics recommended for PD patients in Germany. The lag-time of four quarters means that we used the prescription status from the same quarter of the previous year and excluded all information from the full year before the observation quarter. This allowed us to exclude the possibility that antipsychotics or antidepressants were prescribed for prodromal symptoms of dementia without a prior diagnosis of dementia.

Statistical Analysis

Baseline differences between new male and female PD patients were examined by t test for continuous and Pearson's χ^2 test for categorical variables. We calculated incidence PDD rates and death rates (before PDD) of PD patients by age at first PD diagnosis and current disease severity in terms of HY scale, stratified by sex. We calculated the cumulative incidence function for PDD incidence accounting for death before PDD as competing event. We performed Cox proportional hazards regression models and Fine and Gray competing-risk regression models,[40] taking into account death before PDD as a competing event, to calculate PDD hazard ratios. First, we performed regression models with sex as explaining variable to quantify the sex effect. Second, we performed sex-specific regression models. All models were adjusted for age at first PD diagnosis modelled by a second-degree polynomial function, current disease severity in terms of HY scale,

TABLE 1 *Baseline characteristics of PD study participants, by sex. Source: AOK 2004–2019*

Variable	Men (n = 984)	Women (n = 1211)	*P* value
Age at first PD diagnosis			
Mean age in years	77.1	78.0	
Median age in years (min; max)	77 (65; 95)	77 (65; 100)	<0.001
Mod. HY scale at baseline (share in %)			
0–2.5	22.6	20.5	0.141
3–5	33.3	31.2	
Unknown	44.1	48.3	
Comorbidities			
Cerebrovascular diseases (share in %)	48.8	44.8	0.066
Hypertension (share in %)	90.1	91.7	0.196
Ischemic heart diseases (share in %)	59.9	51.3	<0.001
Hypercholesterolemia (share in %)	37.3	44.7	<0.001
Atrial fibrillation (share in %)	28.7	22.5	0.001
Type 2 diabetes (share in %)	46.4	47.2	0.741
Depression (share in %)	36.3	60.1	<0.001
Psychosis (share in %)	4.3	6.4	0.028
MCI (share in %)	2.2	2.9	0.332

Abbreviations: PD, Parkinson's disease; AOK, Allgemeine Ortskrankenkasse; Mod. HY scale, modified Hoehn and Yahr scale; MCI, mild cognitive impairment; min, minimum; max, maximum.

major cardiovascular diseases and important medications mentioned above. Analysis time started 1 year after the initial PD diagnosis and was measured in months. The time of PDD diagnosis was set to the middle of the relevant quarter, the time of death to the middle of the month of death. Individuals were censored when lost-to-follow-up or at the end of analysis period (end of 2017). Proportionality assumption was tested using Cox models.

All analyses were performed using Stata MP 16.1 (StataCorp LLC, College Station, TX, USA).

This study involved retrospective, anonymized claims data and fell outside the scope of the Declaration of Helsinki and did not require ethical review.

Results

Our analysis sample consisted of 2195 incident PD cases without a dementia diagnosis within the first year after the initial PD diagnosis, summing up to 8443 person-years at risk, of whom 602 individuals died without PDD and 750 individuals got a PDD diagnosis through the end of 2017 (Supplementary Fig. S1). Overall, we had a mean follow-up time of 3.59 years for men and 4.06 years for women.

On average, women (78.0 years) were almost 1 year older than men (77.1 years) at the time of first PD diagnosis (Table 1). In terms of HY scale classification, men

TABLE 2 *Person-years, PDD cases and deaths before PDD, PDD incidence and death rate, and 95% CI for age groups and modified HY scale, by sex. Source: AOK 2004–2019*

	Person-years at risk	PDD cases	IR of PDD per 100 person-years	95% CI of PDD IR		Deaths before PDD	Death rate per 100 person-years	95% CI of death rate	
Total	**8443**	**750**	**8.88**	**8.27**	**9.54**	**602**	**7.13**	**6.58**	**7.72**
Men	3531	332	9.40	8.44	10.47	317	8.98	8.04	10.02
Age group at first PD diagnosis									
65–69	454	28	6.16	4.25	8.92	21	4.62	3.01	7.09
70–74	1226	91	7.42	6.04	9.12	71	5.79	4.59	7.31
75–79	1072	105	9.79	8.09	11.86	90	8.39	6.83	10.32
80–84	554	77	13.90	11.12	17.37	83	14.98	12.08	18.58
85–89	200	23	11.48	7.63	17.28	44	21.97	16.35	29.52
90+	24	8	32.88	16.44	65.74	8	32.88	16.44	65.74
Mod. HY scale									
0–2.5	798	62	7.76	6.05	9.96	57	7.14	5.51	9.25
3–5	1416	177	12.50	10.79	14.49	160	11.30	9.68	13.20
Unknown	1317	93	7.06	5.76	8.65	100	7.59	6.24	9.24
Women	4911	418	8.51	7.73	9.37	285	5.80	5.17	6.52
Age group at first PD diagnosis									
65–69	529	25	4.73	3.20	7.00	11	2.08	1.15	3.76
70–74	1519	85	5.59	4.52	6.92	49	3.23	2.44	4.27
75–79	1518	122	8.04	6.73	9.60	92	6.06	4.94	7.44
80–84	893	111	12.43	10.32	14.98	73	8.18	6.50	10.29
85–89	384	64	16.67	13.05	21.30	44	11.46	8.53	15.40
90+	69	11	15.89	8.80	28.70	16	23.12	14.16	37.74
Mod. HY scale									
0–2.5	983	68	6.92	5.46	8.78	53	5.39	4.12	7.06
3–5	1939	212	10.93	9.55	12.51	131	6.75	5.69	8.02
Unknown	1989	138	6.94	5.87	8.20	101	5.08	4.18	6.17

Abbreviations: PDD, Parkinson's disease dementia; AOK, Allgemeine Ortskrankenkasse; CI, confidence interval; IR, incidence rate; PD, Parkinson's disease; Mod. HY scale, modified Hoehn and Yahr scale.

and women did not differ significantly. Approximately one-fifth were in HY stages 0 to 2.5, and one-third already in stages 3 to 5. Most new PD patients had no documented classification at the time of initial PD diagnosis (men: 44.1%; women: 48.3%). Cerebrovascular diseases, ischemic heart diseases, and atrial fibrillation were more prevalent in men; hypercholesterolemia, depression, and psychosis were more prevalent in women.

The PDD incidence for men (9.5 cases per 100 person-years; 95% confidence interval, [8.4–10.5]) was slightly higher than for women (8.6 [7.7–9.4]), but did not reach significance (Table 2). The older the PD patients were at time of the initial PD diagnosis, the higher was the incidence rate of PDD: at ages 65 to 69 years it was 6.2 in men and 4.7 in women, and at ages 90+ it was 32.9 in men and 15.9 in women.

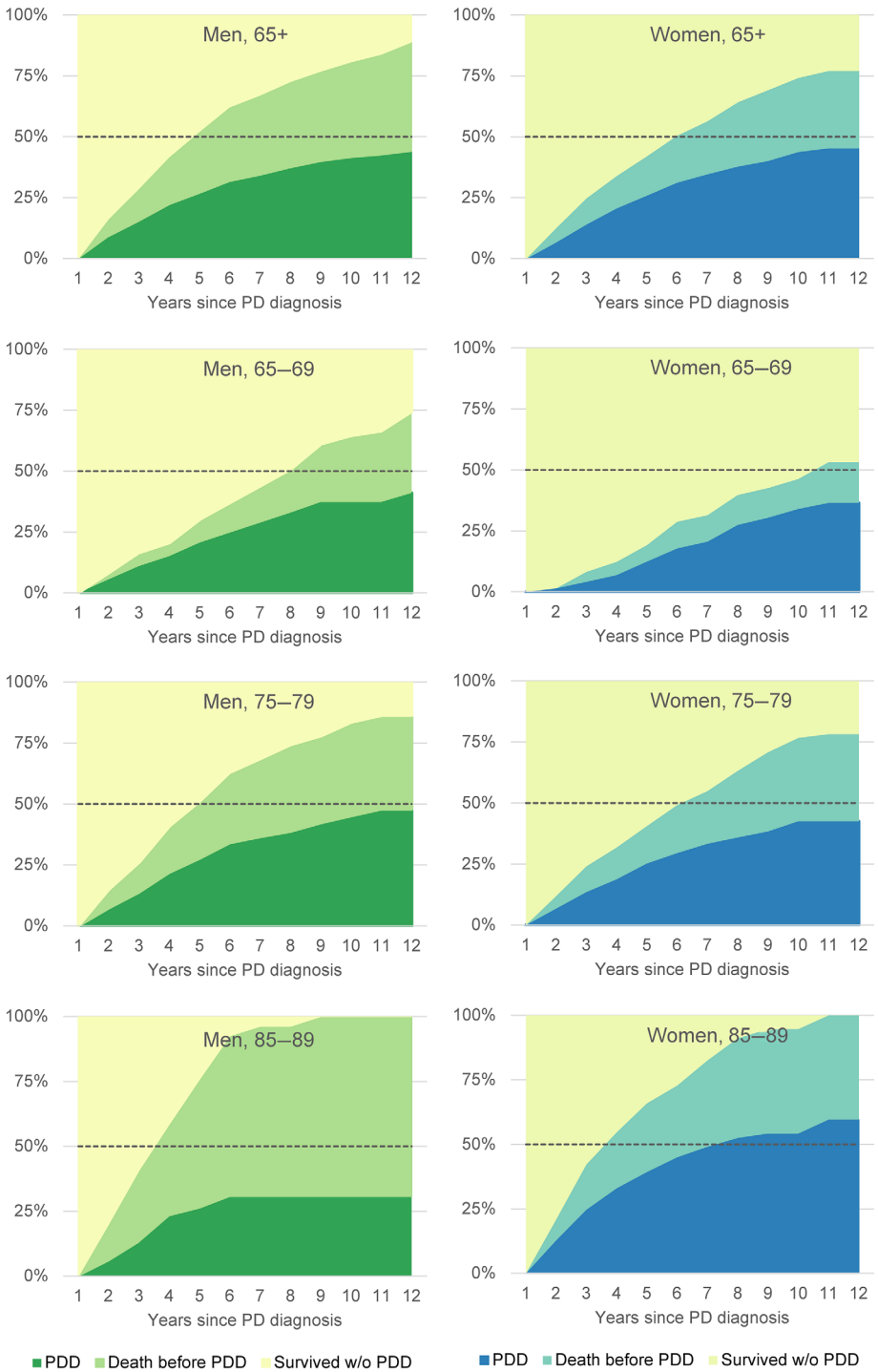

FIG. 1. Cumulative incidence of Parkinson's disease dementia (PDD) and death before PDD, by sex and selected age groups at time of first Parkinson's disease (PD) diagnosis. Source: Allgemeine Ortskrankenkasse 2004 to 2019. [Color figure can be viewed at wileyonlinelibrary.com]

Overall death rate before PDD of men (9.0 per 100 person-years [8.0–10.0]) was significantly higher than for women (5.8 [5.2–6.5]). With the exception of the lowest and the highest age group, men had significantly higher death rates at all ages. Current HY classification was related to PDD incidence, with the lowest incidence rates in HY stages 0 to 2.5 (men: 7.8 [6.1–10.0]; women: 6.9 [5.5–8.8]) and in those without documented classification (men: 7.1 [5.8–8.7]; women: 6.9 [5.9–8.29]). Men in HY stages 3 to 5 had 12.5 [10.8–14.5], women 10.9 cases [9.6–12.5]. Regarding mortality, PD patients in HY stages 0 to 2.5 and without documented classification had comparable death rates with men having always higher death rates than women.

For all ages 65 and older, half of the men had received a PDD diagnosis or had died before PDD 4.5 years after PD onset, compared with 6 years for women. After 12 years, 44% of men and 45% of women had received a PDD diagnosis, 45% of men and 32% of women had died without PDD, and only 11% of men, but 23% of women had survived without PDD (Fig. 1). As expected, the importance of mortality increased with increasing age. In the youngest age group 65 to 69 years, 50% of men either had a PDD diagnosis or had died after 8 years. For women, this was the case after 10 years. In the 85 to 89 age group, half of men and women either had a PDD diagnosis or had died without PDD after 3 years.

Model Results

Tables 3 and 4 show the hazard ratios (HR) and competing-risk hazard ratios (CRHR) for PDD. For each covariate, the proportionality assumption was valid. The adjusted risk of PDD was 18% higher in men than in women (HR = 1.18 [1.02–1.38]). This can be explained by differences in mortality before a possible PDD diagnosis as shown by the competing-risk model, where both sexes had comparable PDD risks (CRHR = 1.02 [0.88–1.19]) (Table 3).

Without controlling for the competing risk of death, the adjusted risk of PDD increased significantly with age in men (age: HR = 1.06 [1.04–1.09], age^2: HR = 1.00 [1.00–1.00]) and women (age: HR = 1.08 [1.06–1.10], age^2: HR = 0.999 [0.996–1.00]). After controlling for death before PDD, the age effect was attenuated in men (age: CRHR = 1.02 [1.00–1.05], age^2: CRHR = 1.00 [1.00–1.00]), but remained significant in women (age: CRHR = 1.05 [1.03–1.07], age^2: CRHR = 0.998 [0.996–1.00]). Controlling for death attenuated the effect of disease severity for men (HY 3–5 vs. 0–2.5: CRHR = 1.31 [0.96–1.78]) but not for women (HY 3–5 vs. 0–2.5: CRHR = 1.46 [1.09–1.96]). Both men and women without documented classification did not differ from those in HY stages 0 to 2.5. Cerebrovascular diseases and MCI significantly increased the risk of PDD in both sexes (cerebrovascular diseases, men: CRHR = 1.26 [1.00–1.59]; women: CRHR = 1.43 [1.16–1.77]; MCI, men: CRHR = 1.97 [1.32–2.95]; women: CRHR = 1.48 [1.06–2.07]) independent of the competing risk of death. When controlling for death, the effect of psychosis was still increased in men (CRHR = 1.57 [0.91–2.71]) and women (CRHR = 1.42 [0.98–2.05]), but did not reach statistical significance. In men, hypercholesterolemia decreased the risk of PDD (CRHR = 0.79 [0.62–0.99]), which was not the case in women (CRHR = 0.87 [0.70–1.07]). In women, the initially detrimental association with atrial fibrillation in the Cox model (HR = 1.29 [1.04–1.61]) was explained by the competing risk of death (CRHR = 1.14 [0.90–1.44]), whereas there was no significant effect in men. The prescription of entacapone (CRHR = 2.24 [1.36–3.67]) and adamantane derivatives (CRHR = 1.42 [1.02–1.98]) in men and the prescription of tertiary amines (CRHR = 1.50 [1.07–2.08]) in women were significantly associated with an increased PDD risk. Further, women had an increased PPD risk after being prescribed clozapine or quetiapine exclusively (CRHR = 2.62 [1.52–4.54]) or in combination with any other antipsychotic drug (CRHR = 1.77 [1.06–2.95]).

Discussion

PDD risk among PD patients differs by sex when controlling for age at PD incidence, disease severity, comorbidities, and medications, with men having a higher PDD risk than women. When accounting for sex-specific survival patterns, men and women do not differ regarding their PDD risk. We find a strong age effect in the

TABLE 3 *Results of Cox and competing-risk regressions models, HR for risk of PDD. Source: AOK 2004–2019*

	Cox model*				Competing-risk model*			
Variables	**HR**	***P* value**	**95% CI**		**CRHR**	***P* value**	**95% CI**	
Sex								
Women	1.00				1.00			
Men	1.18	0.029	1.02	1.38	1.02	0.770	0.88	1.19

Abbreviations: HR, hazard ratio; PDD, Parkinson's disease dementia; AOK, Allgemeine Ortskrankenkasse; CI, confidence interval; CRHR, competing-risk hazard ratios; PD, Parkinson's disease.
*Adjusted for age, PD severity, comorbidities and medications.

TABLE 4 *Results of Cox and competing-risk regressions models, HR for risk of PDD in men (a) and women (b). Source: AOK 2004–2019*

(a) Men	Cox model				Competing-risk model			
Variables	**HR**	***P* value**	**95% CI**		**CRHR**	***P* value**	**95% CI**	
Age at first PD diagnosis								
Age	1.06	<0.001	1.04	1.09	1.02	0.096	1.00	1.05
Age × age	1.00	0.649	1.00	1.00	1.00	0.852	1.00	1.00
Mod. HY scale (Ref. 0–2.5)								
3–5	1.39	0.031	1.03	1.89	1.31	0.089	0.96	1.78
Unknown	0.88	0.440	0.63	1.22	0.84	0.312	0.61	1.17
Comorbidities (Ref. no)								
Cerebrovascular diseases	1.30	0.025	1.03	1.64	1.26	0.055	1.00	1.59
Hypertension	0.96	0.855	0.62	1.49	0.90	0.615	0.58	1.38
Ischemic heart diseases	0.87	0.264	0.68	1.11	0.91	0.477	0.71	1.17
Type 2 diabetes	1.04	0.706	0.83	1.31	1.06	0.616	0.84	1.33
Hypercholesterolemia	0.80	0.056	0.63	1.01	0.79	0.044	0.62	0.99
Atrial fibrillation	0.95	0.653	0.74	1.21	0.81	0.105	0.63	1.04
Depression	1.20	0.153	0.93	1.54	1.22	0.144	0.94	1.58
Psychosis	1.87	0.009	1.17	2.98	1.57	0.102	0.91	2.71
MCI	1.78	0.003	1.21	2.61	1.97	0.001	1.32	2.95
Medication (four quarters lag-time)								
Anti-Parkinson's drugs								
Dopa and dopa derivatives (Ref. no)	1.05	0.705	0.81	1.36	1.00	0.988	0.77	1.31
Dopamine agonists (Ref. no)								
Ergot derivatives only	1.28	0.597	0.51	3.23	1.14	0.791	0.43	3.07
Non-ergot derivatives only	0.99	0.918	0.75	1.30	1.15	0.298	0.88	1.49
Ergot and non-ergot derivatives	1.11	0.799	0.48	2.57	1.55	0.237	0.75	3.20
Entacapone (Ref. no)	1.89	0.039	1.03	3.45	2.24	0.001	1.36	3.67
Tertiary amines (Ref. no)	1.48	0.055	0.99	2.20	1.46	0.059	0.99	2.15
Adamantane derivatives (Ref. no)	1.42	0.038	1.02	1.98	1.42	0.038	1.02	1.98
Antipsychotics (Ref. no)								
Clozapine or quetiapine only	0.48	0.213	0.15	1.53	0.42	0.168	0.12	1.44
Any other antipsychotic	0.87	0.404	0.63	1.20	0.93	0.674	0.68	1.29
Clozapine/quetiapine and any other	0.75	0.545	0.29	1.92	0.56	0.284	0.19	1.62
Antidepressants (Ref. no)	1.01	0.969	0.77	1.32	1.01	0.925	0.76	1.34

(b) Women	Cox model				Competing-risk model			
Variables	**HR**	***P* value**	**95% CI**		**CRHR**	***P* value**	**95% CI**	
Age at first PD diagnosis								
Age	1.08	<0.001	1.06	1.10	1.05	<0.001	1.03	1.07
Age × age	9.99E-01	0.205	9.96E-01	1.00E+00	9.98E-01	0.035	9.96E-01	1.00E+00

(Continues)

TABLE 4 *Continued*

(b) Women	Cox model				Competing-risk model			
Variables	**HR**	***P* value**	**95% CI**		**CRHR**	***P* value**	**95% CI**	
Mod. HY scale (Ref. 0–2.5)								
3–5	1.47	0.007	1.11	1.96	1.46	0.011	1.09	1.96
Unknown	0.98	0.880	0.73	1.31	0.99	0.951	0.73	1.34
Comorbidities (Ref. no)								
Cerebrovascular diseases	1.46	<0.001	1.20	1.79	1.43	0.001	1.16	1.77
Hypertension	0.79	0.290	0.51	1.23	0.82	0.390	0.53	1.28
Ischemic heart diseases	1.05	0.623	0.85	1.30	1.02	0.892	0.81	1.27
Type 2 diabetes	1.12	0.270	0.92	1.36	1.09	0.398	0.89	1.34
Hypercholesterolemia	0.87	0.156	0.71	1.06	0.87	0.187	0.70	1.07
Atrial fibrillation	1.29	0.019	1.04	1.61	1.14	0.275	0.90	1.44
Depression	1.11	0.402	0.87	1.43	1.15	0.279	0.89	1.49
Psychosis	1.48	0.023	1.06	2.09	1.42	0.063	0.98	2.05
MCI	1.53	0.016	1.08	2.16	1.48	0.022	1.06	2.07
Medication (four quarters lag-time)								
Anti-Parkinson's drugs								
Dopa and dopa derivatives (Ref. no)	1.09	0.454	0.87	1.37	1.05	0.658	0.84	1.33
Dopamine agonists (Ref. no)								
Ergot derivatives only	1.30	0.653	0.41	4.13	1.30	0.656	0.41	4.15
Non-ergot derivatives only	1.09	0.468	0.86	1.37	1.23	0.079	0.98	1.56
Ergot and non-ergot derivatives	0.95	0.932	0.30	3.00	1.14	0.831	0.35	3.71
Entacapone (Ref. no)	1.23	0.635	0.53	2.84	1.22	0.683	0.48	3.10
Tertiary amines (Ref. no)	1.42	0.033	1.03	1.96	1.50	0.017	1.07	2.08
Adamantane derivatives (Ref. no)	1.19	0.314	0.85	1.66	1.30	0.123	0.93	1.80
Antipsychotics (Ref. no)								
Clozapine or quetiapine only	2.28	0.001	1.39	3.75	2.62	0.001	1.52	4.54
Any other antipsychotic	1.05	0.664	0.83	1.33	0.97	0.828	0.76	1.24
Clozapine/quetiapine and any other	1.59	0.068	0.97	2.63	1.77	0.029	1.06	2.95
Antidepressants (Ref. no)	1.21	0.111	0.96	1.54	1.23	0.105	0.96	1.57

Abbreviations: HR, hazard ratio; PDD, Parkinson's disease dementia; AOK, Allgemeine Ortskrankenkasse; CI, Confidence interval; PD, Parkinson's disease; CRHR, hazard ratio from competing-risk model; MCI, mild cognitive impairment; Mod. HY scale, modified Hoehn and Yahr scale; Ref., reference.

incidence of PDD in women but not in men, supporting our initial hypothesis that women with PD live long enough to reach old age where they develop dementia, whereas men die before they develop symptoms of dementia.

Using the latest available health claims data for Germany, with a large number of incident PD cases, we estimated the sex- and age-specific transitions to dementia in PD patients, as well as sex-specific differences in risk and protective factors. To differentiate between dementia occurring in PD patients and dementia with Lewy bodies, we used the McKeith criteria.[38] Throughout the study, we monitored a cohort of over 2000

newly diagnosed PD patients ages 65 years or older, ensuring a comprehensive follow-up period of up to 12 years.

Already at baseline, which in our study is incident PD diagnosis, we found sex differences: women were slightly older than men and had more mental conditions, whereas men had more cardiovascular conditions. One third of all new PD cases were already in HY Stage 3 or higher suggesting that a substantial proportion of new PD cases are diagnosed late in the German healthcare system. The proportion was slightly higher in men than in women. This delay in diagnosis comes despite the fact that patients at Stage 3 may still be physically independent, but may already show bilateral symptoms with loss of movement.[39] Our results reflect findings from the United Kingdom, where male sex and presenting the motor phenotype were significantly associated with a delayed diagnosis of PD.[41] In our study, half of the new cases had no classification at HY scale; these probably are mild cases, given that their risk of developing PDD was similar to HY 0 to 2.5.

Although previous studies,[28-30] found that higher ages at time of first PD diagnosis and higher disease severity were associated with an increased PDD risk, we show that this association is attenuated for men once we take death before developing dementia into account. This implies that the most frail men die fast before receiving a dementia diagnosis, whereas women survive to a higher degree than men independent of their age at baseline and PD severity. After 12 years of follow-up from the initial PD diagnosis, 45% of men had died without dementia, but only 32% of women, despite the fact that women were on average older at first PD diagnosis. Aarsland et al[42] showed that the current age is more predictive for the risk of dementia in PD patients than the age of onset of PD, whereas Szeto et al[43] found age and age at onset were not significant. A combined analysis of age at baseline and PD severity found increased PDD risks only for older ages combined with a high disease severity.[44] Hobson and Meara[45] revealed increased PDD risks at higher age of PD onset. PD is associated with increased mortality especially in older age groups.[46,47] We show that over the course of the disease, men always have higher death rates than women, which is reflected in larger changes in parameter estimates when comparing the results of Cox regression with competing-risk regression. Therefore, controlling for the risk of death is mandatory when assessing sex differences in PDD incidence among PD patients.

In men, competing-risk models showed a significantly reduced PDD risk when there was a diagnosis of hypercholesterolemia. This may be an effect of treating hypercholesterolemia with statins, which have been shown to be associated with a lower risk of dementia. However, a review on this association emphasizes the possibility of reverse causation between statin use and dementia risk.[48] Our study did not control for statin use, which should be taken up in future studies.

In both sexes, the presence of cerebrovascular disease during PD course was associated with a significantly increased risk of PDD. Interestingly, women were less likely than men to have cerebrovascular disease at baseline. Probably, more men with cerebrovascular disease at PD incidence die before receiving a PDD diagnosis, whereas more women survive, but then have an increased risk of PDD. As expected, an MCI diagnosis is related to increased risks of subsequent PDD diagnosis. Previous studies also reported high conversion rates from MCI to dementia in PD patients.[49-51]

Atrial fibrillation during PD course was not associated with PDD in men. In women, there was a significant association in the Cox model, which was attenuated when controlling for death. This points at a higher risk of death for PD women when they develop atrial fibrillation, a phenomenon not observed in PD men. This finding is in line with previous studies showing an increased risk of stroke and death in women with atrial fibrillation compared to men.[52,53] Several reasons, including cardiometabolic risk factors, hormones, life style, and quality of treatment, have been discussed to explain the sex differences.[53]

Our models controlled for several medications that are commonly used to treat PD. We differentiated between several ATC classes of anti-Parkinson's drugs, antipsychotics, and antidepressants. To rule out, that medications were prescribed because of early symptoms of dementia, we only looked at associations where at least four quarters had passed from the time of the prescription to the observation quarter. As expected, the first-line treatment with dopa, dopa derivatives, and dopamine agonists was not associated with PDD. The increased PDD risk for entacapone and adamantine derivatives (amantadine) in men and for tertiary amines (eg, biperiden) in women could possibly be associated with their anticholinergic properties, which have previously been shown to increase dementia risk.[54] In addition, adamantine derivatives (amantadine) and entacapone are most commonly used in advanced stages of PD, which can correlate with an increased incidence of PDD. In PD in women, the prescription of the antipsychotics clozapine and quetiapine was associated with an increased risk of PDD. These second-generation antipsychotics are the only antipsychotics recommended for PD patients in Germany. A recent study reported a twofold increased risk of dementia after more than 3 months of antipsychotic treatment with second-generation antipsychotics.[55] In the United States, pimavanserin is already approved by the Food and Drug Administration for PD patients and has been shown to have a better cognitive side effect profile than second-generation antipsychotics.[56]

Although we only looked at prescriptions 1 year before the current observation, the overall relationship between psychosis onset (and treatment threshold) and cognitive impairment remains unclear. This is because of the insidious onset of cognitive decline, which makes it difficult to determine which came first.

Strengths and Limitations

Compared with previous studies on PDD, our sample size is relatively large allowing us to conduct sex- and age-specific analyses with up to 12 years of follow-up. As the data are routinely collected for reimbursement purposes, panel attrition, selection bias, and recall bias because of self-reported conditions and medications can be ruled out. All patients were included regardless of their functional and cognitive abilities, which is particularly important in PD patients who are at a high risk of care need dependency and institutionalization.[57,58] To validate PD and dementia diagnoses, we used established validation strategies that have already been shown to provide sex- and age-specific estimates of PD and dementia incidence comparable to other epidemiologic studies.[3,59,60] We excluded all patients with a diagnosis of atypical parkinsonism and applied the criteria proposed by McKeith et al,[38] which define all new PD cases with a dementia diagnosis within the first year of onset as dementia with Lewy bodies.

Our study is not without limitations. Application of the McKeith criteria may exclude true PDD cases if the PD diagnosis was delayed and dementia symptoms started at least 12 months after the onset of PD. However, in our data, the two diagnoses seem to be closer in time. Half of the newly diagnosed dementia cases were documented within the first year. The guidelines for the diagnosis of PD[61] propose several recommendations for diagnosing PD that can also detect dementia (eg, cranial computed tomography, nuclear magnetic resonance imaging, and positron emission tomography). Therefore, our results may underestimate the true effect sizes. Regarding medication use, we only had information from the outpatient sector. Information on medication use in hospitals was not available. In addition, we do not know whether patients adhered to physician recommendations on medication use. Importantly, a causal interpretation of the effects observed for specific drug compounds should be avoided. Increased PDD risks for certain drugs such as second-line treatments or antipsychotics, may be clinical markers of PD progression rather than representing a biological link between a chemical compound and PDD risk. Other risk factors for PDD, such as sleep behavior or educational level[62] and ethnicity,[44] are missing in the data. The data for the study were collected exclusively from an insurance database and do not provide any clinical information.

Implications

Dementia in PD is an additional factor in caregiver burden and increases the risk of needing care and nursing home placement.[12] Earlier treatment and optimal management of PD and comorbidities, which differ by sex, would not only improve the course of PD, but may also delay the onset of dementia. Medical experts and care providers need to be aware that often male PD patients die before experiencing cognitive decline and dementia, whereas female PD patients survive to those ages where dementia becomes frequent. Early diagnosis opens the possibility of preventing or delaying the transition to dementia through drug and non-drug therapies. For the design of clinical trials, this means, first, that both sexes, men and women, should always be included. Second, because men have a higher mortality rate, a per-protocol design would lead to biased estimates because of higher attrition in men. Therefore, we recommend an intention-to-treat design that includes all individuals from baseline. Third, we recommend conducting stratified analyses by sex because combined models for men and women assume proportional effects of comorbidities and medications, which might not be the case as our analyses show. For the design of observational studies, our results suggest that the difference in mortality between men and women should always be included in the models because Cox models may overestimate the risk of disease when mortality during follow-up is high.[63] For PD patients and their caregivers, it is important to recognize the different risk factors for dementia in men and women. For men, the management of cerebrovascular disease seems to be particularly important, whereas for women, mental comorbidities are of increased importance. Because of the different comorbidity structure of the two sexes, it is possible that men and women would benefit from a sex-specific view of disease progression with tailored therapy, which would need to be demonstrated in clinical trials.

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Data Availability Statement

The scientific research institute of the AOK (WIdO) has strict rules regarding data sharing because of the fact that health claims data are a sensitive data source and have ethical restrictions imposed because of concerns regarding privacy. Anonymized data are available to all interested researchers on request. Interested individuals or an institution who wish to request access to the health claims data of the AOK may contact the WIdO (webpage: http://www.wido.de/, mail: wido@wido.bv.aok.de).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.