RESEARCH ARTICLE

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Estimating the prevalence of Parkinson's disease (PD) and proportions of patients with associated dementia and depression among the older adults based on secondary claims data

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Objectives: While the epidemiology of Parkinson's disease (PD) has been extensively studied, data on the prevalence of PD among the older adults in Germany are scarce, based on small samples, and limited to primary data designs. This study estimated the PD prevalence among the older adults in Germany in 2006 using secondary data.

Methods: We included 815,573 health insurance members aged ≥65 years from all regions in Germany. PD was identified in case of at least one inpatient or outpatient diagnosis. An outpatient diagnosis had to be confirmed by either a subsequent diagnosis or an antiparkinsonian drug within 12 months. PD was also assumed if a first prescription was confirmed by a diagnosis within 12 months. Cases were checked for a diagnosis of dementia or depression.

Results: The standardized prevalence of PD was 1680 (95% confidence interval (CI): 1644–1716) cases per 100,000 persons. The prevalence increased with age and peaked in the age group of ≥90 years (4633 cases; 95% CI: 4227–5068) with higher rates in men (1729; 95% CI: 1684–1776) than in women (1644; 95% CI: 1593–1697). Dementia and depression occurred in 26.6% (95% CI: 25.8–27.5) and 32.6 (95% CI: 31.7–33.5) of PD cases, respectively.

Conclusions: The age-related increase of PD prevalence and the age-specific prevalence estimates are in line with other European studies, stressing the public health relevance related to PD. In addition to the minimization of biases that might occur in primary data studies, further strengths of our findings are the large underlying sample size and the coverage of Germany.

Key words: Parkinson's disease; dementia; depression; epidemiology; secondary data; claims data
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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and is clearly associated with age with a reported prevalence of 41/100,000 in 40- to 49-year-olds and 1903/100,000 in persons over 80 years (Pringsheim *et al.*, 2014) In Europe, the prevalence was estimated at 1800/100,000 in persons over 65 years of age (de Lau *et al.*, 2004; de Rijk *et al.*, 1997). So far, only few studies have estimated the prevalence of PD in Germany. Mostly conducted in the early 1990s, there were localized studies with smaller sample sizes, thwarting the provision of solid prevalence estimates stratified by

age and sex (Evers and Opladen 1994; Kleinhenz *et al.*, 1990; Riedel *et al.*, 2013; Trenkwalder *et al.*, 1995; Vieregge *et al.*, 1991). The occurrence of PD—especially with dementia and depression—has been reported to increase care dependency (Ehret *et al.*, 2009; Riedel *et al.*, 2012), treatment costs (Bach *et al.*, 2012), and the burden of caregivers (Shin *et al.*, 2012). Considering the aging societies, these problems can be expected to substantially aggravate in the future, making a more solid database on the epidemiology necessary. We therefore estimated the prevalence of PD and associated dementia and depression among the older adults based on data from three German statutory health insurance (SHI) providers.

Methods

Data sources

The study was based on the German Pharmacoepidemiological Research Database, which comprises claims data from up to four SHIs, covering more than 17 million insurants throughout Germany of every age (Mikolajczyk *et al.*, 2015). For the present analyses, data from three SHIs were considered, comprising information on more than 8 million insurants. Briefly, German Pharmacoepidemiological Research Database contains individual data including sociodemographics, hospitalizations, diagnoses and procedures in hospital, outpatient care data, and outpatient drug prescriptions. All diagnoses are coded according to the German modification of the International Classification of Diseases, 10th revision (ICD-10-GM). At the time of the study, data were available for the period from January 2004 to December 2007.

Study population

Insurants aged 65 years or older were included if they had a continuous, active minimum insurance period of 365 days beginning in the year 2006 or if they died during the observation period.

Case identification

Cases of PD were ascertained by the ICD-10-GM code G20 and the Advanced Therapeutic Chemical code N04 for antiparkinsonian drugs. PD was identified in case of at least one inpatient or outpatient diagnosis of PD in 2006. To increase certainty of the identification algorithm, outpatient diagnoses had to be confirmed by a subsequent diagnosis of PD or by a prescription of an antiparkinsonian drug within 12 months. PD was also assumed if a first prescription in 2006 was confirmed by a PD diagnosis within 12 months. Cases with secondary parkinsonism (G21) were excluded. Case identification was based on outpatient diagnoses of type "certain" and inpatient main discharge and secondary diagnoses only. Inpatient admission diagnoses as well as outpatient diagnoses of type "suspected," "status post," and "condition excluded" were excluded. Insurants who died during the observation period were included (2.4% of all), regardless whether they met the inclusion criterion of a minimum insurance period of 365 days. The date of first ascertainment of PD in 2006 (inpatient diagnosis, outpatient diagnosis, or prescription) was designated as the index date. Additionally, for each case, the presence of a diagnosis of depression (F32.- and F33.-) or dementia (F00.-, F02.3, F03, and G30.-) was checked within the 365 days of follow up after the case index date.

Study period

Parkinson's disease prevalence was calculated for the year 2006. Because of the case identification, algorithm data until December 2007 were considered.

Statistical analysis

The crude prevalence was calculated by dividing all PD cases with an index date in 2006 by the study population in 2006. The denominator was defined as the mean number of insured persons on 1 January and on 31 December 2006. Using the method of Newcombe and Altman (2001), 95% confidence intervals (CIs) were calculated. Age-specific and sex-specific prevalences were calculated in 5-year age bands and standardized to the German population in 2006 based on data from the German Federal Statistical Office. For standardized prevalences, 95% CIs were calculated following the method by Fay and Feuer (1997). Frequencies of dementia and depression were compared between subgroups with the chi-squared test. All statistical analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Ethics

The use of SHI data for scientific research in Germany is regulated by the Code of Social Law. All involved SHIs and the responsible regulating authorities approved the use of the data for this study. Informed consent was not required by law, because the study was based on pseudonymous data.

Results

We included 815,573 insurants aged ≥65 years with a mean age of 71.8 (median 70, standard deviation 6.2) years. Hereof, 10,596 (1.3%) PD cases were identified, resulting in a crude PD prevalence of 1330/100,000 (95% CI: 1310–1360). The mean age of PD cases was 76.3 (median 76, standard deviation 7.2) years. The age-stratified and sex-stratified prevalences of PD are shown in Table 1.

The prevalence increased with age and peaked in the group of ≥90 years with 4633 (95% CI: 4227–5068) cases per 100,000 persons. In each age group, the prevalence of PD was higher in men than in women (overall: 58% in men). Based on the German population in 2006, we estimated an age-standardized and sex-standardized prevalences of 1680 (95% CI: 1644–1716) PD cases per 100,000 persons in people aged ≥65 years. The total proportions of dementia and depression in PD cases were 27.8% (95% CI: 26.9–28.6) and 32.6 (95% CI: 31.7–33.5), respectively. While the rates of dementia increased with age, the rates of depression ranged between 26.2% and 33.7% across all age groups are considered. Women were afflicted more frequently with dementia (29.6%, 95% CI: 28.2–30.9 vs. 24.5%, 95% CI: 23.5–25.6, $p < 0.0001$) and depression (42.5%, 95% CI: 41.1–44.0 vs. 25.6%, 95% CI: 24.6–26.7, $p < 0.0001$; data not shown).

Discussion

We investigated the prevalence of PD in a population-based sample of patients aged 65 years and older, using data from three large German SHIs. Our estimated prevalence of 1330/100,000 concurs with prevalence estimates from France, the Netherlands, and Spain (de Lau and Breteler, 2006; de Rijk *et al.*, 1997; von Campenhausen *et al.*, 2005). It also dovetails with the pooled prevalence of 1800/100,000 calculated in seven European studies (de Rijk *et al.*, 2000). A review of 39 European studies reported considerably lower estimates (von Campenhausen *et al.*, 2005); however, these were usually not restricted to older persons. Aside from different age distributions in the study populations, the variation in prevalence may also arise from different methods, for example, case finding strategies or diagnostic criteria (de Lau and Breteler, 2006; von Campenhausen *et al.*, 2005).

We are aware of five studies that have determined the prevalence of PD in Germany. Four of them, conducted in the 1990s, ascertained PD cases only in defined regions of Germany. They were insufficiently sized to stratify prevalence by age and sex and varied considerably in the reported prevalences: For rural Bavaria, Trenkwalder *et al.* (1995) reported 713 cases per 100,000 inhabitants over 65 years old, based on 982 participants. For the northern Ruhr area, an estimated prevalence of 12,000/100,000 was based on data from 328 home residents (Evers and Opladen, 1994). Two

Table 1 Prevalence of PD and associated dementia/depression among the older adults

	PD Prevalence, *n*/100,000 (95% CI)			Proportion of patients with comorbidity, % (95% CI)	
	Men	Women	Total	Dementia[a]	Depression[b]
Age group, years					
65–69	677 (643–713)	506 (471–542)	605 (580–631)	12.7 (11.4–14.1)	33.1 (31.2–35.0)
70–74	1286 (1223–1351)	959 (894–1026)	1151 (1105–1198)	19.5 (18.0–21.2)	33.7 (31.8–35.6)
75–79	2368 (2252–2489)	1729 (1620–1845)	2082 (2000–2165)	27.8 (26.1–29.6)	33.0 (31.2–34.9)
80–84	3784 (3559–4020)	2760 (2586–2943)	3221 (3081–3365)	38.9 (36.8–41.1)	32.8 (30.8–34.9)
85–89	4866 (4418–5346)	3806 (3499–4133)	4203 (3947–4472)	46.0 (42.9–49.1)	30.8 (28.0–33.7)
≥90	5057 (4254–5967)	4478 (4013–4982)	4633 (4227–5068)	55.9 (51.4–60.2)	26.2 (22.4–30.3)
Total (≥65 years)	1401 (1366–1436)	1242 (1206–1279)	1331 (1305–1356)	27.8 (26.9–28.6)	32.6 (31.7–33.5)
Age/sex standardized (≥65 years)	1729 (1684–1776)	1644 (1593–1692)	1680 (1644–1716)	—	—

PD, Parkinson's disease; CI, confidence interval; ICD-10, International Classification of Diseases—10th revision.
[a]ICD-10-Codes F00.-, F02.3, F03, and G30.-
[b]ICD-10-Codes F32.- and F33.-

publications estimated a PD prevalence of 183/100,000 in Northern Germany, based on consultation rates at physicians' offices (Kleinhenz *et al.*, 1990; Vieregge *et al.*, 1991). Recently, an overall PD prevalence of 166 PD cases/100,000 persons was reported for the East German capital of Saxony, Dresden, yet without stratifications by sex and age (Riedel *et al.*, 2013).

Our study showed an increasing prevalence of PD with age resembling findings from other studies, but there are also other studies that found a decline of PD prevalence in the highest age groups (de Lau and Breteler, 2006). This corresponds to a previously discussed decline of PD incidence in the highest age groups most likely due to increased diagnostic uncertainty due to comorbidities, diagnostic nihilism, and selective loss to follow-up. Further, the low number of persons of very advanced age destabilizes estimates. We found a slightly higher prevalence of PD in men than in women also supported by other studies (Benito-Leon *et al.*, 2003; Claveria *et al.*, 2002; Errea *et al.*, 1999; Fall *et al.*, 1996; van de Vijver *et al.*, 2001), while in some studies, sex differences were not significant (de Rijk *et al.*, 1997; de Rijk *et al.*, 1995; de Rijk *et al.*, 2000). Neuroprotective effects of estrogens have been considered as a possible explanation, but their role is still uncertain (Benedetti *et al.*, 2001; de Lau and Breteler, 2006).

The rates of dementia and depression in our study population were also in line with estimates from previous systematic reviews (Aarsland *et al.*, 2005; Reijnders *et al.*, 2008). Moreover, these figures also concur with prevalence estimates that have been obtained from a large PD outpatient sample based on a primary data collection (Riedel *et al.*, 2010). This indicates the feasibility of our approach, which was based on secondary (claims) data instead of primary data. Further strengths of our study include its large sample size and the coverage of all regions of Germany. Diagnostic information on hospital or outpatient care as well as on drug dispensations is complete in the database and consistent in quality for all study participants. Selection bias due to non-response can be excluded, and subgroups that are difficult to reach in surveys (e.g., persons of very advanced age or institutionalized persons) could be analyzed. As information on prior disease or drug intake did not depend on memory, recall bias can be ruled out.

Because our study was based on claims data not collected for research purposes, the validity of the diagnostic information has to be considered. In Germany, diagnostic coding in hospitals follows hospital coding guidelines, and coded diagnoses are regularly checked by the Medical Service of the Central Association of Health Insurance Funds (*Medizinischer Dienst der Krankenkassen*). Therefore, high validity is assumed. To take into account the potentially lower validity of outpatient diagnoses, a second outpatient diagnosis of PD or a prescription of an antiparkinsonian drug was required. As repeated physician consultations can be expected, an underestimation of the prevalence is unlikely. However, underestimation could have occurred because of patients who did not seek help from the medical sector. A substantial proportion of patients have been reported to be first diagnosed with PD in door-to-door prevalence surveys (de Lau and Breteler, 2006). Since Germany has universal health insurance coverage and existing studies are mostly from the 1990s, the undiagnosed proportion in Germany is unknown. Comparing our prevalence estimates with other countries must be regarded cautiously, because there is no age and sex standardization for a European population for all these estimates. Hence, differences in the age and sex distributions of the populations studied cannot be eliminated. However, the age-specific PD estimates show rather good agreement with other European studies. Yet it should be kept in mind that an estimated proportion of 10% of patients are diagnosed before the age of 50 years. It is still under debate whether young-onset PD might differ from PD typically occurring beyond the age of 60 regarding etiological and pathophysiological aspects (Dogu *et al.*, 2004). Moreover, as the major public health impact of PD is related to the older adults, we deliberately restricted the analyses to the age range as presented in this study, acknowledging that our results should not be interpreted for younger populations.

Two further potential limitations should be factored when interpreting our results. First, considering the age of the population under study, subjects in higher age groups have a higher probability to die during the observation period, and by implication a lower probability to meet the case definition criteria as described in the section on Methods. For example, subjects who died between the first outpatient diagnosis and the second confirming diagnosis or the subsequent prescription of antiparkinsonian medication would be excluded from the study, leading to a potential underestimation of the PD prevalence. However, the low proportion of deceased insurants in our study sample (2.4% total) might have only slightly influenced the prevalence estimates.

The second limitation lies in the robustness of the applied case definition, which has to be evaluated differentiated, depending on whether the patient was

demented or not. The definition of PD by either two corresponding diagnoses or the combination of a PD diagnosis and the prescription of antiparkinsonian medication can be regarded reliable, because antiparkinsonian drugs are barely used outside the context of PD.

However, for PD cases with dementia, international consensus guidelines require that the cognitive impairment develops 12 months earliest after the onset of PD (McKeith *et al.*, 1996). If the dementia occurs within 1 year after the onset of PD, the diagnosis of Dementia with Lewy bodies (DLB, ICD code G31.82) must be made instead. As we have only analyzed prevalent cases, we cannot exclude that some of our identified PD cases with dementia might have been erroneously diagnosed with PD instead of DLB. However, given the substantially lower incidence rates of DLB of 0.1% per year (Zaccai *et al.*, 2005), as well as the well-established guidelines for the diagnosis of DLB, this proportion can be regarded vanishingly low.

Conflict of interest

E. G. is head of a department that occasionally conducts studies for pharmaceutical industries, including Mundipharma, Bayer, Stada, Sanofi-Aventis, Sanofi-Pasteur, Novartis, Celegene, Otsuka, and GSK. E. G. has been a consultant to Bayer-Schering, Nycomed, Teva, GSK, and Novartis in the past. The present study is not related to these activities. I. L. worked on research projects sponsored by Bayer-Pharma. The present work is unrelated to these grants and relationships. O. R., D. B., and U. A. declare that they have no conflicts of interest.

Key points

- Previous epidemiological studies on PD were mostly based on primary data collections, restricted to regions, limited by small sample sizes and did not factor dementia and depression.
- We conducted a study on the prevalence of PD with dementia/depression using health claims data.
- The rates of PD with and without dementia or depression are in line with previous works. Further strengths of the study are the coverage of an European country and the minimizations of biases that might occur in primary data studies.

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