The association of comorbidity with Parkinson's disease-related hospitalizations

Hommel, Adrianus L.A.J.; Krijthe, Jesse H.; Darweesh, Sirwan; Bloem, Bastiaan R.

DOI
10.1016/j.parkreldis.2022.10.012

Publication date
2022

Document Version
Final published version

Published in
Parkinsonism and Related Disorders

Parkinsonism and Related Disorders 104 (2022) 123–128

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The association of comorbidity with Parkinson's disease-related hospitalizations

Adrianus L.A.J. Hommel [a,b], Jesse H. Krijthe [c], Sirwan Darweesh [d], Bastiaan R. Bloem [d,*]

[a] Primary and Community Care, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Groenhuysen Organisation, Roosendaal, the Netherlands
[c] Delft University of Technology, Pattern Recognition & Bioinformatics, Delft, the Netherlands
[d] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands

A B S T R A C T

Introduction: Unplanned hospital admissions associated with Parkinson's disease could be partly attributable to comorbidities.
Methods: We studied nationwide claims databases and registries. Persons with newly diagnosed Parkinson's disease were identified based on the first Parkinson's disease-related reimbursement claim by a medical specialist. Comorbidities were classified based on the Charlson Comorbidity Index. We studied hospitalization admissions because of falls, psychiatric diseases, pneumonia and urinary tract infections, PD-related hospitalizations-not otherwise specified. The association between comorbidities and time-to-hospitalization was estimated using Cox proportional hazard modelling. To better understand pathways leading to hospitalizations, we performed multiple analyses on causes for hospitalizations.
Results: We identified 18 586 people with newly diagnosed Parkinson's disease. The hazard of hospitalization was increased in persons with peptic ulcer disease (HR 2.20, $p = 0.009$), chronic obstructive pulmonary disease (HR 1.61, $p < 0.001$), stroke (HR 1.37, $p = 0.002$) and peripheral vascular disease (HR 1.31, $p = 0.02$). In the secondary analyses, the hazard of PD-related hospitalizations-not otherwise specified (HR 3.24, $p = 0.02$) and pneumonia-related hospitalization (HR 2.90, $p = 0.03$) was increased for those with comorbid peptic ulcer disease. The hazard of fall-related hospitalization (HR 1.57, $p = 0.003$) and pneumonia-related hospitalization (HR 2.91, $p < 0.001$) was increased in persons with chronic obstructive pulmonary disease. The hazard of pneumonia-related hospitalization was increased in those with stroke (HR 1.54, $p = 0.03$) or peripheral vascular disease (HR 1.60, $p = 0.02$). The population attributable risk of comorbidity was 8.4%.
Conclusion: Several comorbidities increase the risk of Parkinson's disease related-hospitalization indicating a need for intervention strategies targeting these comorbid disorders.

1. Introduction

Parkinson's disease (PD) is more prevalent among older people [1]. As such, age-related comorbidities are frequently present [2]. In persons with PD, the cumulative 5-year incidence of osteoarthritis was 77%, of ischemic heart disease 50%, of cancer 33% and of diabetes mellitus 30% [3]. In persons with PD, those who are elderly and those with comorbidities have a higher risk of being hospitalized [4,5]. However, two key gaps in knowledge remain, namely which comorbidities in particular are associated with a risk of hospitalization, and whether comorbidities are specifically associated with hospitalizations related to common complications in PD.

Hospitalizations can worsen parkinsonian symptoms, cause delirium and reduce the ability for self-care [5–8]. In addition, hospitalizations are an important driver of the economic burden of PD [9]. The vast majority of hospitalizations in PD are caused by complications, such as infections, psychiatric problems, falls and motor problems [4,5,8,10]. Regular outpatient treatment by a neurologist reduces the risk of these specific PD-related hospitalizations [11]. However, better management strategies remain necessary as the number of people with PD will rise exponentially in the coming decades [12].

The mechanisms through which comorbidities cause hospitalizations can be entirely related to the comorbidity and irrespective of the persons state of PD. However, there are at least three pathways through which PD and comorbidities interact to cause hospitalization. First, comorbidities worsen parkinsonian symptoms and may potentially increase PD progression. For example, diabetes mellitus associates with more severe rigidity [13], postural instability/gait difficulty [14] and more severe cognitive impairment [15]. Second, the presence of comorbidities in elderly individuals often indicates frailty, which is the notion of diminished physiological reserve necessary to compensate for disease progression [16]. Frailty associates with hospitalizations in PD [17].

* Corresponding author. Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, PO Box 9101, 6500 HB, Nijmegen, the Netherlands.
E-mail address: Bas.Bloem@radboudumc.nl (B.R. Bloem).

https://doi.org/10.1016/j.parkreldis.2022.10.012
Received 27 June 2022; Received in revised form 19 September 2022; Accepted 9 October 2022
Available online 19 October 2022

Third, the quality of neurological care can be diminished if people with PD also have comorbidities. For example, people can have a reduced adherence and attendance to therapies as a result of competing care interests [18].

Whilst cohort studies have reported on the prevalence of comorbidities and the rate of hospitalizations in PD, they have not differentiated hospitalization admission associated with PD and hospitalizations that were necessitated for other reasons [19,20] Also, cohort studies generally have problems recruiting and retaining older and more frail patients who are at risk for hospitalizations [21]. Presently, measures of comorbidities and hospitalizations are collected in claims databases and administrative registries. Whilst these are not designed for research purposes, they allow for studying nationwide representative samples including people across all age, disease severities and comorbid conditions [22]. We set out to study the association of comorbidities prior to PD-diagnosis with hospitalizations associated with PD using readily available administrative registries and claims-databases. Our central hypothesis is that comorbidities increase the risk of a PD-related hospitalization.

2. Methods

2.1. Overview

We studied registries and claims databases, originally used by health insurance or governmental bodies in the Netherlands. These databases are centrally stored with Statistics Netherlands (Centraal Bureau voor Statistiek) as non-public microdata. The data is deidentified and can be accessed after a certain time period by researchers following strict conditions, such as that no study results can be traced back to an individual person. This is operationalized by the regulation that all frequencies exceed N = 5 and all models have at least 5° of freedom. Consequently, in compliance with the ethical and legal regulations in the Netherlands, no further ethical procedure including obtaining informed consent was needed. Data were available from January 2013 to December 2017. Follow-up time started on the first date on which an individual had a diagnostic code of Parkinson's disease. Follow-up time ended at the first of the following events: death or December 31, 2017. All analysis were run in December 2020.

2.2. Population

We identified all persons for whom medical specialist had claimed reimbursement on the basis of a diagnosis PD. The Dutch claims database collects all reimbursements of medical specialists. These reimbursements are based on categories of diagnosis and treatments. Although these categories are revised yearly by government agencies, in practice, they remain largely the same. The categories are loosely based on the International Classification of Diseases – version 9. For persons with PD, a separate diagnostic category exists that is distinct from persons with other atypical parkinsonism.

We selected persons with first claims, indicating a new diagnosis of PD.

2.3. Determinants

From the same claims database we identified comorbidities. We selected comorbidities that were reported before or at the start-date of PD. To reduce the impact of left-censoring of the data we included persons for whom at least 2 years of data was available before PD diagnosis. To select comorbidities with sufficient severity, we based our selection on the Charlson Comorbidity index, as this index lists diseases that impact survival in the general population [23]. We extracted from the reimbursement data information on myocardial infarction, congestive heart failure, diabetes mellitus, stroke or transient ischemic attack (TIA), peripheral vascular disease, chronic kidney disease, liver failure, cancer, connective tissue disease, chronic obstructive pulmonary disease (COPD), acquired immune deficiency syndrome (AIDS), dementia, paraplegia and peptic ulcer disease. A sum score of comorbidities was calculated to mimic a general marker for multimorbidity.

2.4. Covariables

Age, sex, immigration background and percentile disposable income were included as covariates. Percentile disposable income is a measure of socioeconomic status, of which lower scores associates with increased hospitalizations and more comoribidity [24]. Migration status also associates with higher hospitalization risk and was completely available in the dataset [25]. We obtained age, sex, immigration background and, if available, date of death, from the collective basic administration of the Dutch municipalities (Gemeentelijke Basis Administratie). We added the personal percentile of disposable income, based on tax applications (Integraal Huishoudens Inkomen). All datasets of Dutch statistics can be linked as all entries have a unique personal identification number.

2.5. Outcomes

The main outcome was hospital admission for reasons that are associated with PD, such as falls, pneumonia, urinary tract infection and psychiatric disease. The data did not allow for a differentiation between complications caused by PD or complications caused by other diseases. Complications were acquired from the mandatory nationwide hospital-based disease registration (Landelijke Basisregistratie Ziekenhuiszorg). For this registry, hospital staff is required to report a main reason for hospitalization. We grouped all trauma related reasons for hospitalization in a secondary outcome measure for fall-related hospitalization. Respiratory and urinary tract infections as reason for hospitalization were grouped in a pneumonia-related and urinary tract infection-related hospitalization category. Psychiatric reason for hospitalization included dementia, psychosis and depression, and were grouped in psychiatric-related hospitalization. If hospital staff reported Parkinson's Disease as the main reason for hospitalization without further explanation, we categorized admissions as PD-related hospitalizations-not otherwise specified. If a sufficient number of hospitalizations (which we defined as more than 7 df per determinant) existed for a specific cause (for example falls), we analyzed this outcome separately as a secondary outcome measure. Also, survival was a secondary outcome measure.

2.6. Statistical analysis

For each dataset, duplicate entries were identified and removed. Descriptive analysis was used to report the prevalence of the comorbidities at the time of PD diagnosis and the rates of PD-related hospitalizations. We compared the characteristics of the sample of patients with complete measurements with the sample of patients that has missing values for the disposable income variable. We compared difference between these samples using chi-square tests for categorical variables and the student t-test for numerical variables.

To reduce the risk of overfitting, we tested all comorbidities for univariate effects visually using Kaplan-Meier survival curves and using the log-rank test. Comorbidities with a univariate effect with $p < 0.2$, were included in the multivariate models. We used Cox proportional hazard regression to model the time to first hospitalization and negative binomial regression to model the number of repeat hospitalizations. For the model with repeat hospitalizations, we included persons with a follow-up of at least 2 years to reduce the risk of right censoring. Population attributable risk was calculated using the hazard estimate for the Charlson Comorbidity score, to estimate the total impact of comorbidity. We focused our discussion on findings where the p-value <0.05. No correction for multiple analysis was performed.

3. Results

We identified 18 586 people with newly diagnosed PD, of whom 40.1% were female and 13.8% had an immigration background (see Table 1). The socioeconomic status was comparable to the general population (mean percentile of disposable income = 48.2, sd = 26). The most frequent comorbidities were cancer (17.5%), diabetes mellitus (6.0%) and myocardial infarction (5.4%).

No univariate analysis was possible for paraplegia and AIDS, because of low numbers (number of events <5). The median time to hospitalization following the time of the diagnosis of PD was 577 days. PD-related hospitalizations occurred in 1784 persons (9.3%) (see Table 2). Hospitalizations were most frequently due to falls (904; 51% of PD-related hospitalizations), followed by PD-related hospitalizations-not otherwise specified (408; 23%) and pneumonia (349; 20%). The Kaplan-Meier curves and log-rank test showed differences with $p < 0.2$ of PD-related hospitalization for the following comorbidities: congestive heart failure ($p = 0.04$), diabetes mellitus ($p = 0.14$), stroke or TIA ($p < 0.01$), peripheral vascular disease ($p < 0.01$), chronic kidney disease ($p = 0.18$), liver failure ($p = 0.06$), cancer ($p = 0.05$), connective tissue disease ($p = 0.09$), COPD ($p < 0.01$), dementia ($p = 0.11$), peptic ulcer disease ($p < 0.01$) (see supplemental materials). These were subsequently analyzed in the multivariate models.

Multivariate cox proportional hazard analysis showed decreased time to a PD-related hospitalization in persons with peptic ulcer disease (HR 2.20, $p = 0.009$), COPD (HR 1.61, $p < 0.001$), stroke or TIA (HR 1.37, $p = 0.002$) or peripheral vascular disease (HR 1.31, $p = 0.02$) (see Table 3). Secondary analysis was possible for fall-related hospitalization, PD-related hospitalizations-not otherwise specified, pneumonia-related hospitalization and death (df > 5) (see Table 4). Peptic ulcer disease associated with a decreased time to a PD-related hospitalizations-not otherwise specified (HR 3.24, $p = 0.02$) and pneumonia-related hospitalization (HR 2.90, $p = 0.03$). COPD associated with a decreased the time to a fall-related hospitalization (HR 1.57, $p = 0.003$) and a pneumonia-related hospitalization (HR 2.91, $p < 0.001$). Stroke or TIA associated with a decreased time to a pneumonia-related hospitalization (HR 1.54, $p = 0.03$). Peripheral vascular disease reduced the time to a pneumonia-related hospitalization (HR 1.60, $p = 0.02$).

In addition, the models on fall-related and pneumonia-related hospitalization showed several effects that the model on PD-related hospitalization did not show. First, cancer associated with a decreased time to a fall-related hospitalization (HR 1.22, $p = 0.03$). Second, liver disease (HR 3.17, $p = 0.02$) and chronic kidney disease (HR 1.66, $p = 0.02$) associated with a decreased the time to pneumonia-related hospitalization. The population attributable risk of comorbidity in this model was 8.4% which represents 149 hospitalizations in the current sample. Lastly, repeat hospitalizations was predicted by COPD (exp(beta) = 1.98, $p < 0.001$), connective tissue disease (exp(beta) = 1.86, $p = 0.02$) and cancer (exp(beta) = 1.33, $p = 0.01$).

Table 1
Sample characteristics and frequency of comorbidities.

Characteristic	Value
Sample, number	18 586
Age, mean (sd)	71.8 (10.1)
Female sex, number (%)	7458 (40.1)
Background of immigration, number (%)	2611 (13.8%)
Percentile of disposable income, mean (sd)	48.2 (26)
Comorbidities	
Myocardial infarction, number (%)	1020 (5.4%)
Congestive heart failure, number (%)	583 (3.1%)
Diabetes mellitus, number (%)	1146 (6.0%)
Stroke or TIA, number (%)	966 (5.1%)
Peripheral vascular disease, number (%)	734 (3.9%)
Chronic kidney disease, number (%)	636 (3.4%)
Liver failure, number (%)	74 (0.4%)
Cancer, number (%)	3324 (17.5%)
Connective tissue disease, number (%)	345 (1.8%)
COPD, number (%)	771 (4.1%)
AIDS, number (%)	<20 (0.1%)
Dementia, number (%)	565 (3.0%)
Paraplegia, number (%)	10 (<0.1%)
Peptic ulcer disease, number (%)	77 (0.4%)

Table 2
Frequencies of outcomes.

Outcome	Number (%)	Time to hospitalization in days (median)
Primary outcome		
PD-related hospitalization	1768 (9.3%)	577
Secondary outcomes		
Fall-related hospitalization	904 (4.8%)	608
Pneumonia-related hospitalization	349 (1.8%)	636
Psychiatry-related hospitalization	106 (0.6%)	644
PD symptoms-related hospitalization	408 (2.1%)	630
Death	2304 (12.2%)	649

4. Discussion

This nationwide study revealed that the presence of certain comorbidities prior to PD-diagnosis were associated with PD-related hospitalizations. Specifically, COPD, stroke/TIA, peripheral vascular disease and peptic ulcer disease associated with an increased risk for PD-related hospitalizations when controlled for age, sex, income, migrations status and other comorbidities. However, the effect was modest with a population attributable risk of 8.4% of all hospitalizations.

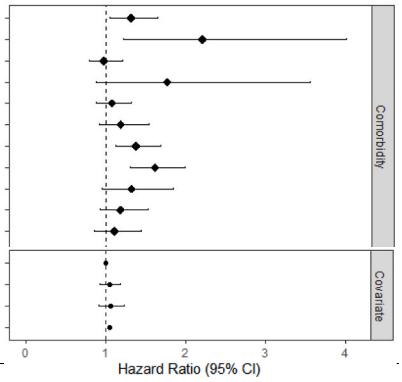
Whilst this is the first study that demonstrates an association between PD-related hospitalizations and stroke in persons with PD, previous studies provide insight on the possible underlying similarities in the etiology [26,27]. Examples of etiologic similarities between PD and stroke are chronic inflammation and oxidative stress [26], or lifestyle similarities, such as the negative impact of a sedentary lifestyle or the beneficial effect of coffee consumption [27]. It is possible that stroke/-TIA of peripheral vascular disease in PD is an indicator of these specific etiological processes. Clinical studies demonstrated several negative outcomes of stroke/TIA and peripheral vascular disease, such as increased postural instability [28], disease progression [29], gait difficulty [30] and cognitive impairment [31]. In our study, secondary analysis revealed an association between pneumonia-related hospitalization and stroke. In both PD and stroke, aspiration caused by dysphagia contributes to a risk of pneumonia [32].

Increased risk on PD-related hospitalizations for those with peptic ulcer disease or COPD was not described in the literature before. Based on clinical reasoning several links could explain the higher risk. For peptic ulcer disease, dopaminergic uptake can be diminished if persons have an helicobacter pylori infection [33], which also increases the risk for peptic ulcer disease [34]. Potentially, lack of dopaminergic uptake increases troublesome "off" time, which associates with adverse outcomes. In support of this, our secondary analysis showed an association between peptic ulcer disease and hospitalizations for PD-related hospitalizations-not otherwise specified. Another explanation for the association of peptic ulcer disease is a screening bias. Patients with troublesome motor fluctuations who are not sufficiently treated with oral dopaminergic treatments can receive Levodopa-Carbidopa intestinal gel therapy [35]. The clinical trajectory for this treatment includes a screening by a gastroenterologist for percutaneous tube placement and consequently these persons with PD are more likely to be diagnosed with peptic ulcer disease. For persons with PD and COPD the increased risk for pneumonia-related hospitalization seems straightforward as both diseases are well-known to increase the risk of pneumonia. Interestingly, in the secondary analysis, COPD also associate with fall-related

Table 3
Multivariate analysis for outcome Parkinson's Disease-related hospitalization.

	Hazard ratio	95% confidence interval		Statistical test	
		Lower bound	Upper bound	Z-score	p-value
Peripheral vascular disease	1.31	1.05	1.64	2.3	0.02
Peptic ulcer disease	2.20	1.22	3.99	2.60	0.009
Myocardial infarction	0.98	0.79	1.21	-0.20	0.84
Liver disease	1.76	0.88	3.54	1.59	0.11
Diabetes mellitus	1.08	0.88	1.32	0.74	0.46
Dementia	1.19	0.92	1.53	1.30	0.19
Stroke or TIA	1.37	1.12	1.68	3.07	0.002
COPD	1.61	1.31	1.99	4.49	<0.001
Connective tissue disease	1.32	0.95	1.84	1.64	0.10
Congestive heart failure	1.18	0.92	1.52	1.32	0.19
Chronic kidney disease	1.11	0.86	1.44	0.80	0.42
Cancer	1.12	0.98	1.27	1.66	0.10
Percentile disposable income	1.00	0.99	1.00	-3.92	<0.001
Female sex	1.05	0.93	1.18	0.81	0.42
Background of immigration	1.06	0.91	1.23	0.75	0.45
Age	1.05	1.05	1.06	15.7	<0.001

Model statistics: n = 15 223 (3 712 observations missing, due to incomplete tax records) number of events = 1 453, concordance = 0.67 (se = 0.007), Likelihood ratio test = 473.5 on 16 df, p < 0.001



Shown are the results of the Cox proportional hazards model. For age, hazard ratio per year increase is shown. For percentile disposable income, hazard ratio per percentile increase is shown. Abbreviations: TIA (Transient Ischemic Attack), COPD (Chronic obstructive pulmonary disease)

Table 4
Secondary multivariate analysis.

	Fall-related hospitalization			PD symptoms-related hospitalization			Pneumonia-related hospitalization		
	Hazard ratio (95% CI)	Statistical test		Hazard ratio (95% CI)	Statistical test		Hazard ratio (95% CI)	Statistical test	
		Z-score	p-value		Z-score	p-value		Z-score	p-value
Determinants									
Peripheral vascular disease	1.21 (0.87–1.68)	1.14	0.26	1.06 (0.63-1.76)	0.21	0.83	1.60 (1.07–2.37)	2.32	0.02
Peptic ulcer disease	1.84 (0.76–4.45)	1.36	0.18	3.24 (1.21–8.72)	2.33	0.02	2.90 (1.08–7.80)	2.11	0.03
Myocardial infarction	1.02 (0.76–1.37)	0.16	0.87	0.90 (0.57–1.40)	−0.47	0.64	0.82 (0.53–1.25)	−0.93	0.35
Liver disease	0.92 (0.23–3.69	−0.12	0.91	2.49 (0.80–7.81)	1.57	0.12	3.17 (1.17–8.56)	2.27	0.02
Diabetes mellitus	1.08 (0.81–1.43)	0.52	0.60	0.81 (0.52–1.27)	−0.91	0.36	1.20 (0.83–1.74)	0.98	0.33
Dementia	1.14 (0.80–1.64)	0.73	0.47	0.99 (0.56–1.78)	−0.02	0.99	1.22 (0.75–2.00)	0.81	0.42
Stroke or TIA	1.30 (0.98–1.73)	1.81	0.07	1.48 (0.98–2.24)	1.89	0.06	1.54 (1.05–2.25)	2.22	0.03
COPD	1.57 (1.17–2.10)	3.02	0.003	0.89 (0.52–1.53)	−0.41	0.68	2.91 (2.10–4.03)	6.46	<0.001
Connective tissue disease	1.49 (0.97–2.28)	1.83	0.07	1.83 (1.00–3.43)	1.97	0.05	0.89 (0.40–2.00)	−0.27	0.78
Congestive heart failure	1.16 (0.81–1.65)	0.80	0.42	1.29 (0.76–2.18)	0.96	0.34	1.23 (0.77–1.94)	0.86	0.39
Chronic kidney disease	0.69 (0.44–1.08)	−1.60	0.11	1.36 (0.83–2.22)	1.21	0.23	1.66 (1.09–2.54)	2.37	0.02
Cancer	1.22 (1.02–1.45)	2.19	0.03	0.97 (0.73–1.27)	−0.24	0.81	1.15 (0.89–1.48)	1.07	0.28
Covariates									
Percentile disposable income	1.07 (1.06–1.08)	−1.95	0.05	1.00 (0.99–1.00)	−1.93	0.05	0.99 (0.99–1.00)	−3.40	<0.001
Female sex	1.33 (1.13–1.56)	3.48	<0.001	0.89 (0.70–1.14)	−0.92	0.36	0.59 (0.46–0.77)	3.87	<0.001
Background of immigration	0.91 (0.73–1.14)	−0.82	0.41	1.38 (1.05–1.81)	2.34	0.02	0.96 (0.70–1.31)	−0.27	0.79
Age	1.00 (1.00–1.00)	13.7	<0.001	1.01 (1.00–1.03)	2.54	0.01	1.06 (1.04–1.07)	8.18	<0.001
Model statistics	n = 15 223 (3712 observations missing, due to incomplete tax records) number of events = 753, concordance = 0.70 (se = 0.010), Likelihood ratio test = −6635 on 16 df, p < 0.001, AIC = 13 302			n = 15 223 (3712 observations missing, due to incomplete tax records) number of events = 370, concordance = 0.59 (se = 0.016), Likelihood ratio test = −3340 on 16 df, p < 0.001, AIC = 6713			n = 15 223 (3712 observations missing, due to incomplete tax records) number of events = 356, concordance = 0.72 (se = 0.014), Likelihood ratio test = −3121 on 16 df, p < 0.001, AIC = 6275		

Shown are the results of the Cox proportional hazards model. For age, hazard ratio per year increase is shown. For percentile disposable income, hazard ratio per percentile increase is shown. Abbreviations: TIA (Transient Ischemic Attack), COPD (Chronic obstructive pulmonary disease.

hospitalizations. Whilst COPD is known to increase risk of falling, this finding has never been described for persons with PD before [36].

Our study showed that comorbidities amounted to a population attributable risk of 8.4%, representing 149 hospitalizations in our sample. This risk is modest when compared to other studies [3,4], but this might reflect that persons in our sample had new-onset PD with at most 5 year follow-up, and were therefore less prone to comorbid diseases. Also, the use of PD-related complications as a cause for hospitalization might have reduced to impact of comorbidity compared to other studies.

This study was not without shortcomings. The set of studied databases were never used for research in PD before, although studies on palliative care and persons with kidney disease were performed [37,38]. Also, one database was used for an analysis of physiotherapy in PD. Whilst the use of claims databases and database registries allowed for a large sample size with high completeness of the data, the data on tax information was not complete. Mainly, information on persons who were never the primary earner of their household was missing and these were mostly women without a personal income. Women with PD have a different phenotype than men, which includes more cardiovascular problems [39] and higher life expectancy [40]. Logically, a higher life expectancy would mean a greater risk of progression to late-stage disease with an increased risk of hospitalizations. We therefore speculate that the exclusion of women resulted in an underestimation of the association between cardiovascular disease and PD-related hospitalizations. In spite of this shortcoming, other subgroups that are often underrepresented in clinical studies were included in our sample, such as persons with a migration background and institutionalized persons. We used readily available databases and registries that were not tailored to our research question. This resulted in challenges, for example, the

comorbidities were not collected using standardized questionnaires. However, our method allows for an easy and reproducible detection of comorbidities without the struggle of recruitment and retainment of participants. The lack of a specific momentary assessment of comorbidities resulted in the risk of left-censoring of the data. We corrected for this risk by only including persons who had at least 2 years of data prior to PD-diagnosis. Using our method, persons who had not visited a specialist for their comorbidity diagnosis 2 years prior to PD-diagnosis were possibly not detected as having a comorbidity. This likely is a modest problem, as we aimed to study comorbidities with sufficient severity. Another limitation is that we relied on diagnostic codes to ascertain cause-specific hospitalizations. Some misclassification of causes may have occurred. Furthermore, we classified hospitalizations due to falls, pneumonia, urinary tract infection and psychiatric disease as PD-related, since these are common complications in PD. However, it is possible that some of these hospitalizations were due to other causes. For instance, a person with PD may fall for a reason not related to PD, such as poor vision due to cataract. Lastly, this study represents the Dutch situation. As health-care systems can differ in reimbursement structures and approaches to hospitalizations, it remains to be seen whether these findings are reproducible in other countries. However, as more countries study their readily available databases the specific strengths and limitations of these databases come to light. For example, in comparison to the US, the Netherlands has an inclusive health care structure surrounding health insurance. As a result, the entire population, whether rich or poor, is included in these databases.

If confirmed, these findings have multiple clinical implications. For example, strategies to reduce the risk of aspiration should be implemented when a person with PD has a stroke/TIA or peripheral vascular disease. Also, more attention should be paid to fall prevention in persons with PD and COPD. These strategies fit into the growing ambitions surrounding personalized medicine [41]. Personalized medicine is an approach to deal with the high clinical heterogeneity of PD by developing tailored-made approaches in care [41]. Examples are decision-aid programs that calculate patient profiles using big data, such as to help clinical decisions making [42]. Or treatment programs that customize treatments based on the genotype of the person with Parkinson [43]. Our study suggest that these programs should account for the effects of comorbidities.

In conclusion, this study demonstrates the specific risk of comorbidities on PD-related hospitalization. Vascular diseases, COPD and peptic ulcer disease show a significant impact on hospitalization and future research should study interventions that treat these comorbidity-effects in persons with PD.

Author's contributions

AH, JK and BRB were involved in the conception and design of the study. AH, JK and SD were involved in the analysis. AH constructed the first draft of the manuscript upon which all authors contributed with critical review. All authors approve of the final version of the manuscript.

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgement

We would like to thank Marjan Meinders, who was involved in the conception of this study. The Radboudumc Centre of expertise for Parkinson & Movement Disorders was supported by a centre of excellence grant of the Parkinson's Foundation. This research was partially funded by a grant from the Netherlands Organization for Scientific Research (TOP Grant 91215076).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.10.012.

References

[1] L.M. de Lau, M.M. Breteler, Epidemiology of Parkinson's disease, Lancet Neurol. 5 (6) (2006) 525–535.
[2] A.D. Macleod, H. Goddard, C.E. Counsell, Co-morbidity burden in Parkinson's disease: comparison with controls and its influence on prognosis, Park. Relat. Disord. 28 (2016) 124–129.
[3] J.C. Pressley, E.D. Louis, M.X. Tang, L. Cote, P.D. Cohen, S. Glied, R. Mayeux, The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism, Neurology 60 (1) (2003) 87–93.
[4] M. Guttman, P.M. Slaughter, M.E. Theriault, D.P. DeBoer, C.D. Naylor, Parkinsonism in Ontario: comorbidity associated with hospitalization in a large cohort, Movement disorders, Off. J. Movement Disorder Soc. 19 (1) (2004) 49–53.
[5] E. Martignoni, L. Godi, A. Citterio, R. Zangaglia, G. Riboldazzi, D. Calandrella, C. Pacchetti, G. Nappi, Comorbid disorders and hospitalisation in Parkinson's disease: a prospective study, Neurol. Sci. 25 (2) (2004) 66–71.
[6] K.L. Chou, J. Zamudio, P. Schmidt, C.C. Price, S.A. Parashos, B.R. Bloem, K. E. Lyons, C.W. Christine, R. Pahwa, I. Bodis-Wollner, W.H. Oertel, O. Suchowersky, M.J. Aminoff, I.A. Malaty, J.H. Friedman, M.S. Okun, Hospitalization in Parkinson disease: a survey of national Parkinson foundation centers, Park. Relat. Disord. 17 (6) (2011) 440–445.
[7] O.H. Gerlach, M.P. Broen, P.H. van Domburg, A.J. Vermeij, W.E. Weber, Deterioration of Parkinson's disease during hospitalization: survey of 684 patients, BMC Neurol. 12 (2012) 13.
[8] H. Woodford, R. Walker, Emergency hospital admissions in idiopathic Parkinson's disease, Mov. Disord. 20 (9) (2005) 1104–1108.
[9] C. Kruse, S. Kretschmer, A. Lipinski, M. Verheyen, D. Mengel, M. Balzer-Geldsetzer, S. Lorenzl, C. Richinger, C. Schmotz, L. Tönges, D. Woitalla, S. Klebe, A. Schrag, R. Dodel, Resource utilization of patients with Parkinson's disease in the late stages of the disease in Germany: data from the CLaSP study, Pharmacoeconomics 39 (5) (2021) 601–615.
[10] M. Braga, M. Pederzoli, A. Antonini, F. Beretta, V. Crespi, Reasons for hospitalization in Parkinson's disease: a case-control study, Park. Relat. Disord. 20 (5) (2014) 488–492, discussion 488.
[11] A.W. Willis, M. Schootman, R. Tran, N. Kung, B.A. Evanoff, J.S. Perlmutter, B. A. Racette, Neurologist-associated reduction in PD-related hospitalizations and health care expenditures, Neurology 79 (17) (2012) 1774–1780.
[12] E.R. Dorsey, T. Sherer, M.S. Okun, B.R. Bloem, The emerging evidence of the Parkinson pandemic, J. Parkinsons Dis. 8 (s1) (2018) S3–s8.
[13] Z. Arvanitakis, R. Wilson, J. Schneider, J. Bienias, D. Evans, D. Bennett, Diabetes mellitus and progression of rigidity and gait disturbance in older persons, Neurology 63 (6) (2004) 996–1001.
[14] V. Kotagal, R.L. Albin, M.L. Muller, R.A. Koeppe, K.A. Frey, N.I. Bohnen, Diabetes is associated with postural instability and gait difficulty in Parkinson disease, Park. Relat. Disord. 19 (5) (2013) 522–526.
[15] N.I. Bohnen, V. Kotagal, M.L. Muller, R.A. Koeppe, P.J. Scott, R.L. Albin, K.A. Frey, M. Petrou, Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease, Park. Relat. Disord. 20 (12) (2014) 1394–1398.
[16] E. Tenison, E.J. Henderson, Multimorbidity and frailty: tackling complexity in Parkinson's disease, J. Parkinsons Dis. 10 (s1) (2020) S85–s91.
[17] D.S. Abraham, T.P. Pham Nguyen, A.W. Willis, Claims-Based Frailty and Outcomes: Applying an Aging Measure to Older Adults with Parkinson's Disease, Mov Disord, 2021.
[18] S. Mendorf, O.W. Witte, H. Zipprich, T. Prell, Association between nonmotor symptoms and nonadherence to medication in Parkinson's disease, Front. Neurol. 11 (2020), 551696.
[19] L.E. Pressley Jc, M.X. Tang, L. Cote, P.D. Cohen, S. Glied, R. Mayeux, The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism, Neurology 60 (1) (2003) 87–93.
[20] C.L. Leibson, D.M. Maraganore, J.H. Bower, J.E. Ransom, C. O'Brien P, W. A. Rocca, Comorbid conditions associated with Parkinson's disease: a population-based study, Movement disorders, Off. J. Movement Disorder Soc. 21 (4) (2006) 446–455.
[21] A.D. Macleod, R. Henery, P.C. Nwajiugo, N.W. Scott, R. Caslake, C.E. Counsell, Age-related selection bias in Parkinson's disease research: are we recruiting the right participants? Park. Relat. Disord. 55 (2018) 128–133.
[22] B.R. Bloem, J.H.L. Ypinga, A. Willis, C.G. Canning, R.A. Barker, M. Munneke, N. M. De Vries, Using medical claims analyses to understand interventions for Parkinson patients, J. Parkinsons Dis. 8 (1) (2018) 45–58.
[23] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (5) (1987) 373–383.
[24] R. Antonelli-Incalzi, C. Ancona, F. Forastiere, V. Belleudi, A. Corsonello, C. A. Perucci, Socioeconomic status and hospitalization in the very old: a retrospective study, BMC Publ. Health 7 (2007) 227.
[25] R.H. Glazier, M.I. Creatore, A.A. Cortinois, M.M. Agha, R. Moineddin, Neighbourhood recent immigration and hospitalization in Toronto, Canada, Can. J. Public Health 95 (3) (2004) I30–I34.

[26] J. Potashkin, X. Huang, C. Becker, H. Chen, T. Foltynie, C. Marras, Understanding the links between cardiovascular disease and Parkinson's disease, Mov. Disord. 35 (1) (2020) 55–74.
[27] B.R. Kummer, I. Diaz, X. Wu, A.E. Aaroe, M.L. Chen, C. Iadecola, H. Kamel, B. B. Navi, Associations between cerebrovascular risk factors and Parkinson disease, Ann. Neurol. 86 (4) (2019) 572–581.
[28] S.M. Ebersbach G, J. Müller, G. Ransmayr, G. Wenning, W. Poewe, Dysequilibrium in idiopathic Parkinson disease. The effect of cerebrovascular comorbidity, Nervenarzt 73 (2) (2002) 162–165.
[29] Y.Y. Li Hj, Y. Chen, H.Y. Liang, Vascular risk factors aggravate the progression of Parkinson's disease: a five-year follow-up study in Chinese patients, Int. J. Clin. Exp. Med. 8 (6) (2015) 9897–9903.
[30] V. Kotagal, R.L. Albin, M.L. Muller, R.A. Koeppe, S. Studenski, K.A. Frey, N. I. Bohnen, Advanced age, cardiovascular risk burden, and timed up and go test performance in Parkinson disease, J. Gerontol. Series A Biol. Sci. Med. Sci. 69 (12) (2014) 1569–1575.
[31] A. Pilotto, R. Turrone, I. Liepelt-Scarfone, M. Bianchi, L. Poli, B. Borroni, A. Alberici, E. Premi, A. Formenti, B. Bigni, M. Cosseddu, E. Cottini, D. Berg, A. Padovani, Vascular risk factors and cognition in Parkinson's disease, J. Alzheim. Dis. : JAD 51 (2) (2016) 563–570.
[32] I. Suttrup, T. Warnecke, Dysphagia in Parkinson's disease, Dysphagia 31 (1) (2016) 24–32.
[33] H. Liu, W. Su, S. Li, W. Du, X. Ma, Y. Jin, K. Li, H. Chen, Eradication of Helicobacter pylori infection might improve clinical status of patients with Parkinson's disease, especially on bradykinesia, Clin. Neurol. Neurosurg. 160 (2017) 101–104.
[34] A. Lanas, F.K.L. Chan, Peptic ulcer disease, Lancet 390 (10094) (2017) 613–624.
[35] N. Vijiaratnam, C.M. Sue, Levodopa-carbidopa intestinal gel: 'dismantling the road blocks of a journey, Intern. Med. J. 48 (4) (2018) 472–474.
[36] A. Hakamy, C.E. Bolton, J.E. Gibson, T.M. McKeever, Risk of fall in patients with COPD, Thorax 73 (11) (2018) 1079–1080.
[37] Horsselenberg Nielen, Korevaar Heins, Nierschade zorgt voor meer ziekenhuisopnamen en sterfte bij patiënten met type 2 diabetes, Nivel, 2022.
[38] M. Oosterveld, A. Reyners, M. Heins, M. Boddaert, Y. Engels, A.v.d. Heide, B. Onwiuteaka-Philipsen, R. Verheij, A. Francke, Factsheet 1: Kenmerken van de populatie en gebruik van ziekenhuis en huisartsenzorg, Nivel, 2020.
[39] M. Picillo, A. Nicoletti, V. Fetoni, B. Garavaglia, P. Barone, M.T. Pellecchia, The relevance of gender in Parkinson's disease: a review, J. Neurol. 264 (8) (2017) 1583–1607.
[40] H.G. Seo, S.J. Byun, B.M. Oh, S.J. Park, Ten-Year Relative Survival from the Diagnosis of Parkinson's Disease: A Nationwide Database Study, J Am Med Dir Assoc, 2020.
[41] B.R. Bloem, W.J. Marks Jr., A.L. Silva de Lima, M.L. Kuijf, T. van Laar, B.P. F. Jacobs, M.M. Verbeek, R.C. Helmich, B.P. van de Warrenburg, L.J.W. Evers, J. intHout, T. van de Zande, T.M. Snyder, R. Kapur, M.J. Meinders, The Personalized Parkinson Project: examining disease progression through broad biomarkers in early Parkinson's disease, BMC Neurol. 19 (1) (2019) 160.
[42] L. van den Heuvel, R.R. Dorsey, B. Prainsack, B. Post, A.M. Stiggelbout, M. J. Meinders, B.R. Bloem, Quadruple decision making for Parkinson's disease patients: combining expert opinion, patient preferences, scientific evidence, and big data approaches to reach precision medicine, J. Parkinsons Dis. 10 (1) (2020) 223–231.
[43] S.A. Schneider, R.N. Alcalay, Precision medicine in Parkinson's disease: emerging treatments for genetic Parkinson's disease, J. Neurol. 267 (3) (2020) 860–869.