RESEARCH ARTICLE

Care of Late-Stage Parkinsonism: Resource Utilization of the Disease in Five European Countries

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ABSTRACT: Background: Parkinson's disease (PD) is a neurodegenerative disease that leads to progressive disability. Cost studies have mainly explored the early stages of the disease, whereas late-stage patients are underrepresented.

Objective: The aim is to evaluate the resource utilization and costs of PD management in people with late-stage disease.

Methods: The Care of Late-Stage Parkinsonism (CLaSP) study collected economic data from patients with late-stage PD and their caregivers in five European countries (France, Germany, the Netherlands, UK, Sweden) in a range of different settings. Patients were eligible to be included if they were in Hoehn and Yahr stage >3 in the *on* state or Schwab and England stage at 50% or less. In total, 592 patients met the inclusion criteria and provided information on their resource utilization. Costs were calculated from a societal perspective for a 3-month period. A least absolute shrinkage and selection operator approach was utilized to identify the most influential independent variables for explaining and predicting costs.

Results: During the 3-month period, the costs were €20,573 (France), €19,959 (Germany), €18,319 (the Netherlands), €25,649 (Sweden), and €12,156 (UK). The main contributors across sites were formal care, hospitalization, and informal care. Gender, age, duration of the disease, Unified Parkinson's Disease Rating Scale 2, the EQ-5D-3L, and the Schwab and England Scale were identified as predictors of costs.

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Conclusion: Costs in this cohort of individuals with late-stage PD were substantially higher compared to previously published data on individuals living in earlier stages of the disease. Resource utilization in the individual sites differed in part considerably among these three parameters mentioned.

Key Words: cost-of-illness; Parkinson's disease; resource utilization; late-stage parkinsonism

Parkinson's disease (PD) is the second most common neurodegenerative disorder. In Western Europe, there are approximately 830,000 individuals with PD, including ~120,000 in France, ~160,000 in Germany, ~30,000 in the Netherlands, ~20,000 in Sweden, and ~115,000 in the UK.[1] Margaret Hoehn and Melvin Yahr (HY) classified the disease into five stages, with stages 4 and 5 describing the late stages.[2] In these stages persons with PD (PwPD) have to cope with increasing impairment, which manifests in motor and nonmotor features.[3-5] PwPD have a reduced health-related quality of life (HRQoL), which is negatively influenced by both motor and nonmotor symptoms.[6] In particular, the latter have a considerable negative effect in the late stages of the disease.[7-9]

The estimated annual costs of the disease in Europe are €14 billion.[10] There are a varying number of cost studies in the five included countries that have shown annual costs of €4716–€20,060 per patient, depending on the cost assessment, study population, and reference year (see Appendix A1).[11-18] Several studies outside these countries provide implications for resource use in European health-care systems, with costs ranging from €5240 to €19,640.[19-22] The proportion of direct costs was reported to be between 47% and 84%.[13,16-22] Previous studies from the five countries showed overall higher costs with increasing disease severity according to HY.[12-18] However, with 5%–40% (range: 5–46 patients), the proportion of late-stage patients included was rather small compared to the proportion of early-stage patients (HY stages 1–3).[13-19,21,23,24] The previously published studies in this disease stage indicated a higher need for care with increased caregiver burden[25,26] and higher resource utilization, especially through hospitalization and institutionalization.[12,13,16,17,19,21,27,28]

The present study aims to provide detailed insights into the resource utilization and drivers of costs in the late stages of the disease across several European countries.

Patients and Methods

Study Design

The Care of Late-Stage Parkinsonism (CLaSP) study is a longitudinal multicentre cohort study of late-stage PwPD and their caregivers from six European countries. Detailed information on the clinical study can be found elsewhere.[29] The aim of the overall study was to examine the health and social care needs, provision, and cost of care of late-stage PwPD, who are often underserved and do not attend specialist centers. To form this target group, we utilized various methods to include patients who are not under regular specialist follow-up. The centers contacted general practitioners, hospitals, nursing homes, patient advocate groups, and self-help groups. The study sites included neurology, care of the elderly, and palliative care settings. Extensive efforts were made to recruit individuals from non-specialist settings, from primary care and nursing homes where this was feasible.

Inclusion and Exclusion Criteria

Patients were eligible for the study when they were in the *on* state and fulfilled one of the two criteria: disease duration of at least 7 years and HY stage 4 or 5 or significant disability according to the Schwab and England Scale (≤50%). The *on* state was determined based on the time when the patient took his or her last anti-parkinsonian medication and the report of the patient and the caregiver about the patient's best motor activity. Patients with secondary parkinsonism (normal pressure hydrocephalus or drug-induced parkinsonism, except if persisting even if the causative drug is discontinued) were excluded. The analysis used only baseline data.

Clinical Measures

The disease-specific condition of PwPD was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS).[2,30,31] Patients' HRQoL was measured using the EQ-5D-3L, which assesses five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[32] The score ranges from less than 0 (equivalent to death) to 1 (perfect health state) and measures a total of 3^5(=243) different health states. The UK time trade-off (TTO) value set was used to ensure comparability across countries.[32]

Resource Use and Cost Estimation

Resource use was assessed using a standardized questionnaire adapted to the respective health-care system and completed by the patients or caregivers. Unit costs were based on national sources and guidelines (Appendix A2)

and were calculated from a societal perspective for the year 2016. We selected a 3-month period to enhance recall accuracy and provide a comprehensive overview of respondents' resource utilization. Direct resource utilization was observed in the following areas: (1) outpatient medical visits (consulted physicians and other health-care professionals); (2) ancillary therapy (physiotherapy, occupational therapy, speech training, visits of a nurse, and further therapy); (3) inpatient hospitalization; (4) inpatient and outpatient rehabilitation clinic; (5) medical devices and consumables; (6) formal care (care inside home, day care outside home, respite and short-term care admission, and nursing home care); (7) medication; and (8) informal care. Indirect costs were measured using the human capital approach for absence from work due to illness, as well as incapacity to work, unemployment, early retirement, and reduced working hours due to PwPD. A description of further assumptions can be found in Appendix C.

Recruitment

In France, the study predominantly enrolled outpatients and inpatients at a tertiary referral center, under the close monitoring of investigators. In Germany, patients were primarily recruited from specialist hospital clinics, where care was provided by an investigator. In addition, a fraction of patients were recruited from patient organizations. In the Netherlands, recruitment occurred at secondary and tertiary neurology clinics and elderly care clinics, mostly under the care of the investigator. In Sweden, patients were mainly recruited from Lund University Hospital outpatient clinics and specialty care centers, all under the supervision of a neurologist or the care of an elderly consultant. In the UK, most participants were recruited from primary care/general practices, community pharmacies, PD charities, PD volunteer database, nursing homes, care of the elderly, and neurology outpatient clinics.

Statistical Analysis

Statistical analysis was executed with IBM SPSS Statistics version 26.0.0.0 (IBM, Armonk, New York). The objective was to obtain detailed insights into the use of resources in the respective sites through exploratory analysis. Due to the non-normal and positively skewed distribution of most parameters, bias-corrected and accelerated bootstrap 95% confidence intervals with 1000 replications were calculated in addition to the arithmetic means. Non-parametric Kruskal-Wallis or Mann-Whitney *U* test was used to compare groups. A least absolute shrinkage and selection operator (LASSO) approach was utilized to identify the most influential independent variables for explaining and predicting (total) costs. This analysis was conducted using the glmnet package in R. The relaxed LASSO technique[33] helps in selecting relevant covariates for the model without shrinking the estimated coefficients. The penalty strength for LASSO was determined through an advanced cross-validation technique implemented in the glmnet package. The potential cost drivers, considered as independent variables, were examined using a generalized linear model (GLM) with a gamma-distributed dependent variable and a log link function. Country-specific data were evaluated for utilization quantity and costs as well as disease severity.

Results

Patient Characteristics

The baseline information of the PwPD group is presented in Table 1. A total of 592 PwPD were included, with 76 persons from France, 228 from Germany, 78 from the Netherlands, 106 from Sweden, and 104 from the UK. The proportion of female participants within the study population ranged from 41% (UK) to 46% (France, the Netherlands). The mean age of the PwPD ranged from 74.1(±8.4) years in Germany to 78.3(±6.9) years in Sweden. Disease duration varied from 12.64(±8.14) years in Germany to 17.68(±9.72) years in France. The mean health state measured by the EQ-5D-3L ranged from 0.51(±0.20) in France to 0.65 (±0.18) in the UK. It decreased in all countries as the HY stage increased.

Resource Utilization

Resource utilization differed notably between national health-care sites (Table 2). At the French, German, and UK sites, over 85% of PwPD had at least one outpatient medical visit in the past 3 months. At the Dutch and Swedish sites, however, proportions were 73.1% and 67.9%, respectively. At the French site, an average patient received more ancillary therapeutic interventions than PwPD in other countries. Furthermore, the proportion of PwPD receiving this form of therapy was higher at the French (94.7%), German (78.2%), and Dutch (85.9%) sites than at the Swedish (52.8%) and UK sites (52.9%).

The hospitalization rates also differed considerably. Regarding the PwPD who had a hospital stay, the rate was 6.4% in the Netherlands, 15.1% in Sweden, and 16.3% in the UK; however, this rate was 30.3% and 52.4% in France and Germany, respectively. Except for PwPD at the German sites, the utilization rate of formal care in the home environment was relatively similar. There were also differences between sites in the utilization of formal care in the form of nursing homes. In Germany and the UK, only 5.7% and 3.8% of PwPD, respectively, were cared for in a

TABLE 1 *Baseline information about patients' characteristics*

Parameter	Country	Disease severity (Hoehn and Yahr stage)			Total
		≤Stage 3	Stage 4	Stage 5	
Number of patients (%)	France	5 (6.58)	44 (57.89)	27 (35.53)	76
	Germany	14 (6.14)	142 (62.28)	72 (31.58)	228
	The Netherlands	11 (14.10)	39 (50.00)	28 (35.90)	78
	Sweden	0 (0.00)	79 (74.52)	27 (25.47)	106
	UK	11 (10.58)	62 (59.62)	31 (29.81)	104
Gender (% female)	France	40.00	43.18	51.85	46.05
	Germany	42.86	42.96	41.67	42.54
	The Netherlands	18.18	53.85	46.43	46.15
	Sweden	—	41.77	40.07	41.51
	UK	36.36	41.94	41.94	41.35
Age (mean [SD])	France	75.00 (9.27)	77.25 (6.72)	78.52 (7.93)	77.55 (7.29)
	Germany	75.43 (9.69)	73.37 (9.01)	75.17 (6.61)	74.06 (8.39)
	The Netherlands	71.91 (6.91)	75.85 (6.61)	78.36 (10.07)	76.19 (8.23)
	Sweden	—	78.06 (6.88)	78.96 (7.12)	78.29 (6.92)
	UK	76.64 (0.56)	74.84 (11.88)	78.03 (6.86)	75.98 (10.41)
Duration of the disease (y [SD])	France	14.80 (7.95)	16.93 (9.25)	19.44 (10.75)	17.68 (9.72)
	Germany	8.93 (5.31)	13.83 (8.27)	11.01 (7.93)	12.64 (8.14)
	The Netherlands	16.45 (8.94)	15.85 (6.60)	16.75 (11.64)	16.26 (8.92)
	Sweden	—	15.42 (6.87)	16.07 (6.50)	15.58 (6.76)
	UK	14.36 (2.87)	13.35 (5.82)	14.42 (5.65)	13.78 (5.52)
UPDRS 1—mentation, behavior, and mood (mean [SD])	France	8.00 (1.00)	6.23 (2.94)	8.22 (3.50)	7.05 (3.20)
	Germany	2.79 (2.23)	4.69 (2.67)	6.50 (3.21)	5.14 (3.00)
	The Netherlands	5.09 (2.39)	4.41 (2.85)	6.25 (2.81)	5.17 (2.87)
	Sweden	—	4.04 (2.89)	6.07 (3.37)	4.56 (3.14)
	UK	4.09 (3.83)	3.57 (2.55)	6.33 (3.48)	4.45 (3.22)
UPDRS 2—activities of daily living (mean [SD])	France	24.20 (6.46)	27.05 (6.58)	31.37 (6.29)	28.39 (6.80)
	Germany	19.14 (5.22)	24.31 (6.71)	33.32 (6.55)	26.84 (7.99)

(Continues)

TABLE 1 *Continued*

Parameter	Country	Disease severity (Hoehn and Yahr stage) ≤Stage 3	Stage 4	Stage 5	Total
	The Netherlands	24.27 (7.25)	26.92 (6.83)	30.96 (4.35)	28.00 (6.50)
	Sweden	—	22.70 (5.49)	30.30 (4.16)	24.63 (6.14)
	UK	21.45 (7.05)	23.15 (6.55)	30.27 (6.85)	25.06 (7.45)
UPDRS 3—motor examination (mean [SD])	France	36.60 (10.26)	45.29 (13.90)	60.22 (14.62)	50.22 (15.95)
	Germany	36.14 (16.66)	43.20 (13.88)	62.87 (15.32)	48.98 (17.36)
	The Netherlands	40.36 (11.62)	35.90 (11.35)	59.21 (12.30)	44.90 (15.90)
	Sweden	—	35.38 (12.10)	59.59 (11.99)	41.55 (16.02)
	UK	32.64 (9.29)	43.49 (12.95)	54.70 (14.09)	45.62 (14.52)
UPDRS 4—complications of therapy (mean [SD])	France	4.40 (3.78)	5.36 (3.44)	4.67 (3.34)	5.05 (3.40)
	Germany	2.00 (3.72)	5.39 (3.91)	3.64 (3.08)	4.63 (3.79)
	The Netherlands	4.91 (2.17)	5.82 (3.82)	4.64 (2.90)	5.27 (3.33)
	Sweden	—	4.53 (2.93)	4.78 (2.64)	4.59 (2.84)
	UK	6.73 (4.50)	6.10 (3.88)	5.73 (4.39)	6.06 (4.07)
EQ-5D-3L (mean [SD])	France	0.69 (0.09)	0.50 (0.20)	0.48 (0.21)	0.51 (0.20)
	Germany	0.80 (0.16)	0.63 (0.18)	0.58 (0.16)	0.63 (0.18)
	The Netherlands	0.75 (0.14)	0.64 (0.20)	0.49 (0.18)	0.62 (0.20)
	Sweden	—	0.61 (0.18)	0.50 (0.19)	0.59 (0.19)
	UK	0.68 (0.22)	0.65 (0.18)	0.59 (0.16)	0.65 (0.18)

Parameter	Country	Disease severity (Schwab and England Scale) 0%	10%	20%	30%	40%	50%	60%	70%	80%	Total
UPDRS 6—Schwab and England Scale (number of patients [%])	France	—	11 (14.47)	20 (26.32)	23 (30.26)	10 (13.16)	9 (11.84)	2 (2.63)	1 (1.32)	—	76
	Germany	15 (6.58)	24 (10.53)	34 (14.91)	55 (24.12)	35 (15.35)	56 (24.56)	7 (3.07)	2 (0.88)	—	228
	The Netherlands	—	11 (14.47)	20 (26.32)	23 (30.26)	10 (13.16)	9 (11.84)	2 (2.63)	1 (1.32)	—	76
	Sweden	—	4 (3.77)	21 (19.81)	18 (16.98)	26 (24.53)	25 (23.58)	7 (6.60)	3 (2.83)	2 (1.89)	106
	UK	1 (0.96)	16 (15.38)	19 (18.27)	23 (22.12)	10 (9.62)	15 (14.42)	9 (8.65)	8 (7.69)	3 (2.88)	104

Abbreviations: SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 2 *Selected resource use per patient in the 3-month period*

Resource parameter		Statistic	Country				
			France	Germany	The Netherlands	Sweden	UK
Outpatient medical visits		Patients with utilization (%)	85.6	88.6	73.1	67.9	87.5
		Mean number of visits (BCa 95% CI)*	4.4 (3.2; 5.9)	4.9 (4.1; 5.7)	2.6 (1.8; 3.5)	1.3 (1.0; 1.7)	2.5 (2.0; 3.1)
Ancillary therapy		Patients with utilization (%)	94.7	78.2	85.9	52.8	52.9
		Mean number of visits (BCa 95% CI)*	71.8 (61.9; 82.4)	25.3 (22.2; 28.3)	19.5 (15.6; 23.3)	6.8 (4.3; 9.6)	3.9 (2.0; 6.6)
Hospitalization		Patients with utilization (%)	30.3	52.4	6.4	15.1	16.3
		Mean length of stay (days) (BCa 95% CI)*	4.2 (2.4; 6.7)	7.2 (5.9; 8.5)	0.2 (0.0; 0.5)	1.2 (0.7; 1.8)	1.2 (0.6; 1.9)
Formal care services	Care inside home	Patients with utilization (%)	31.6	5.7	28.2	25.5	26.0
		Mean number of days (BCa 95% CI)*	24.0 (16.1; 32.5)	2.5 (1.1; 4.1)	18.3 (11.3; 25.9)	16.6 (9.9; 24.3)	16.2 (9.9; 23.1)
	Day care outside home	Patients with utilization (%)	9.2	10.2	9.0	10.4	8.7
		Mean number of days (BCa 95% CI)*	1.5 (0.4; 2.7)	2.6 (1.3; 4.1)	2.2 (0.7; 3.9)	1.7 (0.5; 3.2)	1.4 (0.5; 2.5)
	Respite/short-term care admission	Patients with utilization (%)	0.1	7.1	1.3	10.4	11.5
		Mean number of days (BCa 95% CI)*	0.6 (0.0; 1.5)	1.0 (0.5; 1.6)	0.8 (0.0; 2.4)	3.0 (1.3; 5.2)	1.4 (0.6; 2.4)
	Nursing home	Patients with utilization (%)	32.9	5.7	51.3	38.7	3.8
		Mean number of days (BCa 95% CI)*	28.1 (18.9; 38.2)	5.1 (2.6; 7.8)	46.2 (36.6; 57.5)	33.0 (25.4; 41.5)	2.1 (0.1; 4.6)
Informal care		Patients with utilization (%)	98.7	82.5	89.7	83.8	94.7
		Mean number of hours per day (BCa 95% CI)*	9.5 (7.9; 11.1)	9.7 (8.8; 10.7)	4.8 (3.3; 6.4)	5.2 (3.8; 6.6)	8.2 (7.0; 9.7)

Abbreviation: CI, confidence interval.
*95% bias-corrected and accelerated bootstrap CI.

TABLE 3 *Resource use per patient in the 3-month period (€)*

Cost parameter	Country	Mean	Bootstrap BCa 95% CI* Lower	Bootstrap BCa 95% CI* Upper	Median	Total costs (%)
Total costs (direct costs, indirect costs, and no informal care costs)	France	12,198	9966	14,732	9753	100
	Germany***	9657 (8995)	8362	11,193	7453	100 (100)
	The Netherlands	13,678	11,517	15,854	15,519	100
	Sweden	14,097	12,007	16,039	11,367	100
	UK	4405	3086	5951	1105	100
Direct costs**	France	11,961	9857	14,409	9688	98.1
	Germany***	8749 (8033)	7332	10,400	6567	90.6 (89.3)
	The Netherlands	13,220	11,255	15,854	15,519	96.7
	Sweden	13,719	11,958	15,570	10,604	97.3
	UK	3598	2392	5163	893	81.7
Costs—outpatient medical visits	France	212	153	291	152	1.7
	Germany***	177 (179)	153	203	124	1.8 (2.0)
	The Netherlands	276	209	347	192	2.0
	Sweden	290	229	357	284	2.1
	UK	291	223	367	195	6.6
Costs—ancillary therapy	France	1492	1269	1725	1339	12.2
	Germany***	639 (641)	566	711	434	6.7 (7.1)
	The Netherlands	648	524	793	556	4.7
	Sweden	808	558	1102	137	5.7
	UK	71	36	116	15	1.6
Costs—hospital	France	2759	1522	4208	0	22.6
	Germany***	4964 (4992)	4039	5955	1386	51.4 (55.5)
	The Netherlands	158	33	308	0	1.2
	Sweden	821	474	1181	0	5.8
	UK	1070	512	1758	0	24.3
Costs—rehabilitation	France	17	0	35	0	0.1
	Germany***	206 (214)	99	328	0	2.1 (2.4)
	The Netherlands	1530	722	2448	0	11.2
	Sweden	167	36	365	0	1.2
	UK	626	11	1400	0	14.2
Costs—medical devices	France	1336	1168	1506	1402	11.0
	Germany***	188 (192)	140	237	0	1.9 (2.1)
	The Netherlands	67	47	96	17	0.5
	Sweden	78	41	121	4	0.6
	UK	38	19	60	0	0.9

(Continues)

TABLE 3 *Continued*

Cost parameter	Country	Mean	Bootstrap BCa 95% CI* Lower	Bootstrap BCa 95% CI* Upper	Median	Total costs (%)
Costs—formal care	France	2891	2155	3846	2196	23.7
	Germany***	697 (689)	478	956	0	7.2 (7.7)
	The Netherlands	9189	7609	10,777	15,260	67.2
	Sweden	10,631	8821	12,558	8716	75.4
	UK	1225	697	1833	0	27.8
Costs—medication	France	3252	2098	4461	1078	26.7
	Germany***	1070 (1127)	820	1321	545	11.1 (12.5)
	The Netherlands	1352	683	2157	151	9.9
	Sweden	924	706	1185	556	6.6
	UK	277	209	377	183	6.3
Costs—indirect	France	237	118	474	0	1.9
	Germany***	962 (962)	606	1337	0	10.0 (10.7)
	The Netherlands	458	63	852	0	3.3
	Sweden	264	88	440	0	2.7
	UK	807	304	1372	0	18.3
Costs—informal care (separated from other costs)	France	8375	6971	9801	13,412	
	Germany***	10,964	10,012	11,952	13,289	
	The Netherlands	4641	3156	6181	1021	
	Sweden	11,552	8613	14,482	4471	
	UK	7751	6553	9057	7437	

Abbreviation: CI, confidence interval.
*95% bias-corrected and accelerated bootstrap CI.
**Direct costs arising from the sum of outpatient medical visits, ancillary therapy, hospital stays, rehabilitation, medical devices, formal care, and medication.
***Values within brackets represent the mean of the five imputed datasets. Values without brackets represent the results of the complete case analysis.

nursing home. However, at the French (32.9%), Dutch (51.3%), and Swedish sites (38.7%), the share was considerably higher. The French (9.5 h), German (9.7 h), and UK (8.2 h) caregivers spent, on average, the most informal care time per day. However, in the Netherlands (4.8 h) and Sweden (5.2 h), this number was considerably lower.

Utilization Costs

As a result of the utilization of resources, the overall results for the examined sites also diverged in terms of costs (Table 3). The highest total costs without informal care per patient were found in the Swedish (€14,097) and Dutch sites (€13,678). Slightly lower costs were found at the French (€12,198), followed by the German (€8995) and UK sites (€4405). At both the Swedish (€10,631; 75.4%) and Dutch sites (€9189; 67.2%), the largest contributor to costs was formal care. At the French site, hospitalization (€2759; 22.6%), formal care (€2891; 23.7%), and medication (€3252; 26.7%) each accounted for approximately one-quarter of the costs. Of these medication costs, €2165 was related to the treatment of PwPD with subcutaneous application of apomorphine (Fig. 1). At the German site, hospitalization (€4992; 55.5%) was the largest parameter. At the UK site, approximately half of the costs were attributable to hospitalization (€1070; 24.3%) and formal care (€1225; 27.8%). Overall, direct costs outweighed indirect costs at all sites. However, the share of direct costs was higher at the French (98.1%), Dutch (96.7%), and Swedish sites (97.3%) than at the German (89.3%) and UK sites (81.7%). The separately examined informal care costs were €8375 at the French, €10,964 at the German, €4641 at the Dutch, €11,552 at the Swedish, and €7751 at the UK sites. In terms of utilization costs in relation to HY stages, results can be seen in Appendix Table A2.

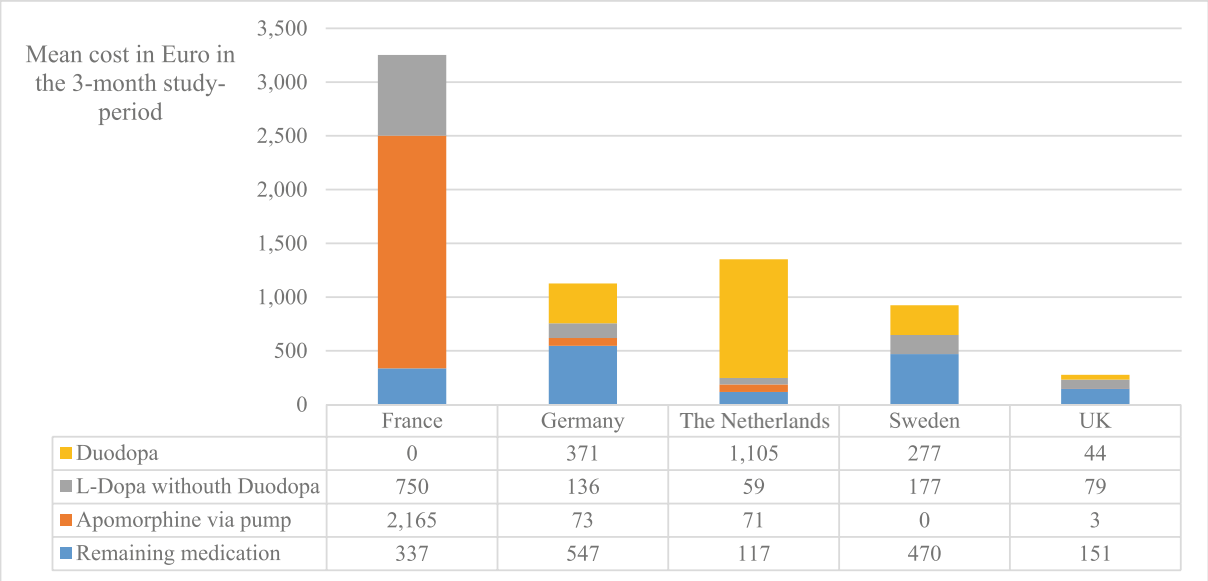

FIG. 1. Mean cost for medication per patient in euros in the 3-month period with separate listing of levodopa and apomorphine via pump.

TABLE 4 *Multiple regression analysis identified cost-driving factors*

	Total costs				
			95% CI		
Parameter	**β***	**Exp (β)****	**Std. error**	**CI lower**	**CI upper**
Intercept	10.829		0.680	9.450	12.172
The Netherlands	0.171	1.186	0.161	−0.137	0.495
Sweden	0.445	1.560	0.131	0.188	0.708
UK	−0.856	0.425	0.136	−1.119	−0.585
Gender, male	−0.161	0.851	0.102	−0.364	0.039
Age	−0.022	0.978	0.006	−0.034	−0.011
Duration of the disease (y)	0.025	1.026	0.006	0.013	0.038
UPDRS 2—activities of daily living	0.011	1.011	0.010	−0.008	0.031
EQ-5D-3L	−0.399	0.671	0.287	−1.010	0.198
UPDRS 6—Schwab and England Scale	−0.009	0.991	0.004	−0.018	−0.000

Abbreviations: CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale.
*The regression coefficient indicates that a value of 0 signifies no influence, whereas a value >0 (<0) indicates positive (negative) influence.
**The factor by which the predicted costs are influenced when the parameter is increased by 1 while keeping the other parameters unchanged.

Regression Analysis

When including all variables (country, gender, age, duration of the disease, UPDRS 1 to 4, EQ-5D-3L, HY stage, Schwab and England Scale), the relaxed LASSO selects for gender, age, the duration of the disease, UPDRS 2, the EQ-5D-3L, and the Schwab and England Scale (Table 4). In terms of countries, France served as the reference value. Although Germany showed no effect compared to France, the Netherlands and Sweden showed higher costs and the UK lower costs. Within the final model, further interpretation of the estimated coefficients using *P*-values is not recommended because uncertainty from the selection process through the LASSO is ignored.[34] The estimated coefficients can be interpreted as follows. An increase of one unit in the parameter increases the total cost by exp(β) if the other parameters remain unchanged. Accordingly, an increase in age by 1 year decreases costs by approximately

2.2%, and an increase in the duration of the disease by 1 year increases costs by approximately 2.6%. If the UPDRS 2—Activities of Daily Living score increases by one unit, costs increase by approximately 1.1%. Similarly, a one-unit increase in the Schwab and England Scale decreases costs by approximately 1.0%. A 0.1 increase in EQ-5D-3L reduces the expected cost by about 4%. Male patients have an expected cost reduction of 14.9% compared to females.

Discussion

The CLaSP study aims to provide the first detailed insights into the resource use and costs of late-stage parkinsonism within five European countries. Previous studies with a small number of late-stage patients indicated (1) a higher need for care and (2) an increased caregiver burden due to the progression of PD.[25,26] Furthermore, (3) higher resource utilization has been reported thus far, especially due to increased hospitalization and institutionalization.[12,13,16,17,19,21,27,28] When comparing our results to those of previous studies, we extrapolated the costs to a one-year period, if necessary. Because there were methodological differences, study-specific cost assessments are listed in Appendix Table A1.

Total Costs in the CLaSP Study and Their Comparison with the Relevant Literature

The mean total costs in a 3-month period (extrapolated to 1 year) without informal care were €12,198 (€48,792) in France, €8995 (€35,980) in Germany, €13,678 (€54,712) in the Netherlands, €14,097 (€56,388) in Sweden, and €4405 (€17,620) in the UK. When informal care costs were included, the costs increased by €8375 (€33,500) in France, €10,964 (€43,856) in Germany, €4641 (€18,564) in the Netherlands, €11,552 (€46,208) in Sweden, and €7751 (€31,004) in the UK.

The largest study in Europe that used a homogenous approach collected the illness costs for PwPD in Austria (12% HY 4, 4% HY 5), the Czech Republic (2%, 1%), Germany (5%, 1%), Italy (4%, 0%), Portugal (8%, 0%), and Russia (19%, 4%). The total costs per year, including informal care, ranged from €5240 in Russia to €19,640 in Austria.[19] Other previous studies in the five countries showed mean total costs between €4716 and €20,060, but no informal care costs were considered. In small patient populations, costs for the late stages were estimated to be up to €47,200 per year.[11-18] The comparison with the listed studies shows that the observed costs of the countries examined in the CLaSP study, except for the UK site, were in the upper range of the calculated costs of the late stages. In addition to the methodological differences, different price levels and the possible statistical spread caused by the small number of observations may be due to increasing resource consumption as a result of medical progress.[16] Furthermore, recruitment strategies will have contributed to differences between populations.

Hospitalization Costs

Extrapolated to 1 year, the hospital costs were €11,036 at the French and €19,968 at the German sites, thus constituting major components of the costs. In contrast, hospitalization costs were much lower at the Dutch (€632), Swedish (€3284), and UK sites (€4280). Previous studies observed lower costs in Germany from €1747 to €2406[17,18] and other European countries from €220 to €3520.[19,21]

Formal Care Costs

The highest formal care costs were observed at the Dutch (€36,756 per year) and Swedish sites (€42,524 per year). At the French site, these costs amounted to €11,564. At the French (62%), Dutch (85%), and Swedish sites (76%), these costs were mainly caused by institutional care in nursing homes. At the German (€2756) and UK sites (€4900), where fewer participants were in nursing homes, the formal care costs were lower. Overall, this shows a moderate to very strong increase compared to the formal care costs in Europe previously determined, which ranged from €120 to €2120.[19]

Costs of Medication

Extrapolated to 1 year, the medication costs were €13,008 at the French, €4508 at the German, €5408 at the Dutch, €3696 at the Swedish, and €1108 at the UK sites. Except for the French site, the medication costs were largely comparable to the previously published costs for other less severely ill PwPD, which ranged from €1065 to €6512.[15,18-21] Notably, at the French site, 17.1% of the PwPD were treated with an apomorphine pump. As a consequence, 67% of the medication costs were incurred by this particular type of drug alone. At the German (3.1%), Dutch (1.3%), Swedish (0%), and UK sites (4%), considerably fewer PwPD were treated with an apomorphine pump.

Indirect Costs

Within all sites, direct costs outweighed indirect costs (81.7–98.1% of costs excluding informal care). Indirect costs related to lost work time for PwPD in the examined countries were essentially lower than those in previous studies, in which their proportion was from 16% to 53%,[13,16-22] mainly because the majority of PwPD in the CLaSP study had already reached retirement age. Nevertheless, it is known that PwPD drop out of the labor market earlier than the general

population,[35] and indirect costs are likely to be higher in those with earlier disease onset.

Country-Specific Remarks on the Major Cost Components

The results demonstrated the relevance of hospitalization and patient care to the disease costs. More PwPD had a hospital stay at the German (52.4%) and French sites (31.6%) than at the Dutch (6.4%), Swedish (15.1%), and UK sites (16.3%). Furthermore, the mean length of stay per patient was higher at the German and French sites than at the other three sites. Although some of this difference may reflect recruitment bias at participating sites, there are known differences between countries in hospital admission rates: hospital discharges among the 75–79-year-olds in the general population are higher in France (48,403 per year per 100,000) and Germany (61,487) than in the Netherlands (27,701), Sweden (38,513) and the UK (32,307).[36] The lengths of stay of hospitalized PwPD in this study and the general age-matched population[36] also differed among the French (13.8 days vs. 10.2 days), German (13.6 vs. 9.2), UK (7.5 vs. 9.2), Swedish (7.3 vs. 5.5), and the Dutch sites (3.8 vs. 5.5). Speculatively, the existing PD network in the Netherlands may have been able to reduce hospitalizations through the expertise and focused collaboration of physicians, PD nurse specialists, therapists, and caregivers.[37] In general, larger data samples have shown thus far that PwPD have an approximately 1.45 times higher hospitalization rate than the population of the same age.[38,39]

Patient care was investigated in terms of both formal and informal care. Overall, multiple formal care services were assessed, and it was found that PwPD were cared for differently at the sites studied. At the French (31.6%), Dutch (28.2%), Swedish (25.5%), and UK sites (26.0%), a substantial proportion of PwPD received regular formal care at their own homes. German PwPD received this type of care considerably less often (5.7%), which may be explained in part by the monetary incentive to substitute formal home care with informal care.[40] Furthermore, at the French (32.9%), Dutch (51.3%), and Swedish sites (38.7%), the proportion of PwPD living in a formal care facility such as a nursing home was considerably higher at the German (5.7%) and UK sites (3.8%). This cannot solely be explained by the capacity of beds in related facilities in the respective countries, which was 995 beds in nursing homes per 100,000 in France, 1120 per 100,000 in Germany, 1062 per 100,000 in the Netherlands, 1325 per 100,000 in Sweden, and 845 per 100,000 in the UK in 2014/2013.[41] An analysis based on data from approximately 6.7 million insured persons with different statutory health insurances in Germany estimated that approximately 21% of German PD patients live in a nursing home.[42] In the UK, the observed proportion (3.8%) of patients in nursing homes in the CLaSP study was comparable to that of a less severely ill patient population (2–6%).[15] However, in a study of medication use by late-stage PD patients in the UK, approximately 24% were living in a nursing home.[43] Accordingly, the investigated population may underrepresent patients in nursing homes at the German and UK sites. Generally, it can be assumed that over time the number of nursing home placements of PD patients increases,[22] which is supported by data indicating their high use of this parameter in France, the Netherlands, and Sweden.

The proportion of PwPD in nursing homes is also reflected in the informal care time. At the Dutch (4.8 h) and Swedish sites (5.2 h), informal care time per day was substantially lower than that at the German (9.7 h) and UK sites (8.2 h). At the French site (9.5 h), however, the mean informal care time was quite similar to that at the German site, even though PwPD received a relatively high amount of formal care. Comparing informal care time with the published literature is difficult because there is no consensus on which factors should be included; therefore, informal care time is assessed differently.[44,45] Previous studies provided varying results, which also depended on the respective health system and the patient population. Klietz and colleagues[46] observed 5.3 to 5.5 h/day in Germany; McCrone observed 3.5 to 3.8 h/day in the UK,[15] and Campenhausen and colleagues observed 1.4 to 8 h/day in Austria, the Czech Republic, Germany, Italy, Portugal, and Russia.[19] Accordingly, a differentiated conclusion must be drawn regarding informal care. The progression of the disease led to an increase in the need for care. It appeared that there were health-care systems in which relatives compensated for this effect considerably more. This especially seems to apply to the French, German, and UK sites than to the Dutch and Swedish sites. However, it is unclear how much this observation is influenced by the presumably underrepresented number of nursing home residents in the German and UK sites. First, it seems plausible that informal care time would decrease with higher institutional placement of PwPD, although the support of an informal caregiver is unlikely to become completely dispensable.[47] However, this relationship could not be observed as strongly in the French PwPD as in the Dutch and Swedish PwPD. Second, the situation among late-stage PwPD cannot be generalized. The Dutch site has a lower burden of informal care when the disease progresses more. Thus, daily informal care time is reduced from 6.6 h/day in HY 4 to 1.2 h in HY 5. At the French site, there is also a decrease in informal care time between the two late stages from a mean of 10.4 to 8.0 h/day. At the Swedish site, informal care time remains constant, whereas at the German and UK sites, informal care time increases between the two late stages of the disease. The higher need for care among PwPD in the late stages of

the disease is thus compensated to varying degrees by the sites. This is reflected in particular in the utilization of formal care, which increased considerably in all countries as the disease progressed but counteracted increased informal care to different extents.

Cost-Driving Predictors

The inclusion of countries as a categorical variable in the regression analysis allows us to make a more generalizable interpretation of the remaining coefficients. When analyzing the age of the patients, an expected reduction in costs of 2.2% with each additional year of age appears contradictory at first. However, this relationship is plausible considering that the indirect costs can occur only before retirement and that the duration of the disease is also an explaining variable in the model. A negative correlation between total costs and patient age[16,18] and a positive correlation with the duration of the disease[15,17] were also observed in other studies. In addition, costs increase with an increase in UPDRS 2—Activities of Daily Living. Although not all studies examine this variable in terms of its cost-driving effect, the relationship between a decrease in the ability to manage activities of daily living and rising costs has been demonstrated several times.[12,17,18] Contrary to our model, previous studies showed lower expected costs for female patients compared with male patients.[15,18] This could be caused by the fact that women are more likely to be informal caregivers than men[15] and informal care costs were not considered within our model. A correlation between an increase in costs and a decrease in the quality of life was also shown and is plausible. Both the Schwab and England Scale and the HY Scale represent disease severity. The relaxed LASSO selects the Schwab and England Scale, whereas the HY scale is not selected. The reason for this is probably that our model includes only patients with late-stage disease, among whom the Schwab and England Scale, with its several gradations, allows a more sensitive differentiation.

Influence of Recruitment Strategies

The recruitment strategies employed in each country might contribute to the observed resource utilization across the national health-care sites. Especially, the more diverse recruitment of patients in the UK may have led to a cohort with slightly milder disease severity and less likely utilization of specialized health-care services compared to the cohorts recruited from the other sites. The higher hospitalization rates in France and Germany in contrast to the Netherlands, Sweden, and the UK could be associated with the recruitment of patients from specialized hospital clinics and tertiary centers, where patients may be more likely to have medical conditions requiring hospitalization. Nevertheless, the different recruitment settings do not diminish the significance of the identified cost-driving factors, as within the GLM the influences of recruitment are represented by the country variable.

The strength of this study lies in the large sample size and the inclusion of a variety of settings. The recruitment process facilitated the inclusion of patients from diverse health-care settings. Nevertheless, the results demonstrate the costs of different aspects of care of PD at this stage and cost drivers across countries. Furthermore, it should be noted that the PwPD included in HY stages ≤3 are not representative of the early stages of the disease. Although they were not classified into a late stage based on the HY Scale, they showed considerable impairment according to the Schwab and England Scale. Therefore, the patients in HY stages ≤3 in this study may differ from early-stage patients in other studies.

In summary, although our results do not allow for conclusive results on the effectiveness of specific care models, they demonstrate that although informal care costs are a strong cost driver at this disease stage, this is matched by costs of formal care in care homes and hospitalizations in other countries, whereas the use of medication and medical devices, with the exception of the tertiary referral center in France, ancillary therapy, rehabilitation, and outpatient visits, represents a relatively low cost in this population. Prospective studies should address whether methods to support informal caregivers and outpatient services can reduce hospitalizations and admission to care homes with improved quality of life and comparable or lower costs.

Ethics Approval

All study sites received approval from their local ethics committee before the start of the study; all patients gave their written informed consent before study participation.

The CLaSP study is being conducted in compliance with the Helsinki Declaration; that is, detailed oral and written information is given to the patients and their informants to ensure that the patient fully understands the potential risks and benefits of the study. The study protocol was approved by the local ethics committees of all participating study sites (London: Camden and Islington NRES Committee 14/LO/0612; Bordeaux: South West and Overseas Protection Committee III [South West and Overseas Protection Committee] 2014-A01501-46; Lisbon: Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014-275; Lund: Regional Ethical Review Board in Lund, Sweden [JPND HC 559-002, Protocol code: Dnr 2014/561]; Marburg: Ethik-Kommission bei der Landesärztekammer Hessen [Ethics Commission at the State Medical Association Hesse] MC 309/2014; Munich: Ethikkommission bei der LMU München [Ethics committee at the LMU München] 193-14; Nijmegen: Radboud

universitair medisch centrum, Concernstaf Kwaliteit en Veiligheid, Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen [Radboud University Medical Center, Group Staff Quality and Safety Human Research Committee, Arnhem-Nijmegen region] DJ/CMO300).

Consent to Participate

Participants (patients and their caregivers) were included in the study after their written informed consent was obtained. In case the patient lacked the capacity to give consent to the study due to severe cognitive impairment, the decision on study participation was made by a legal guardian or consultee, depending on the ethical and legal requirements at each site. All participants (patients and caregivers) can withdraw from the study at any point in time without any negative implications.

Consent for Publication

All authors have read the final manuscript and consented to the publication.

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Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on a reasonable request.

References

1. Dorsey ER, Elbaz A, Nichols E, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 2018;17(11):939–953. https://doi.org/10.1016/S1474-4422(18)30295-3
2. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17(5):427–442. https://doi.org/10.1212/wnl.17.5.427
3. Coelho M, Ferreira J, Rosa M, Sampaio C. Treatment options for non-motor symptoms in late-stage Parkinson's disease. Expert Opin Pharmacother 2008;9(4):523–535. https://doi.org/10.1517/14656566.9.4.523
4. Hely MA, Morris JGL, Reid WGJ, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20(2):190–199. https://doi.org/10.1002/mds.20324
5. Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. Lancet Neurol 2006;5(1):75–86. https://doi.org/10.1016/S1474-4422(05)70285-4
6. Hinnell C, Hurt CS, Landau S, Brown RG, Samuel M. Nonmotor versus motor symptoms: how much do they matter to health status in Parkinson's disease? Mov Disord 2012;27(2):236–241. https://doi.org/10.1002/mds.23961
7. Rosqvist K, Odin P, Lorenzl S, et al. Factors associated with health-related quality of life in late-stage Parkinson's disease. Mov Disord Clin Pract 2021;8(4):563–570. https://doi.org/10.1002/mdc3.13186
8. Gallagher DA, Lees AJ, Schrag A. What are the most important non-motor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord 2010;25(15):2493–2500. https://doi.org/10.1002/mds.23394
9. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 2011;26(3):399–406. https://doi.org/10.1002/mds.23462
10. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(10):718–779. https://doi.org/10.1016/j.euroneuro.2011.08.008
11. Lökk J, Borg S, Svensson J, Persson U, Ljunggren G. Drug and treatment costs in Parkinson's disease patients in Sweden. Acta Neurol Scand 2012;125(2):142–147. https://doi.org/10.1111/j.1600-0404.2011.01517.x
12. LePen C, Wait S, Moutard-Martin F, Dujardin M, Ziégler M. Cost of illness and disease severity in a cohort of French patients with Parkinson's disease. Pharmacoeconomics 1999;16(1):59–69. https://doi.org/10.2165/00019053-199916010-00006
13. Hagell P, Nordling S, Reimer J, Grabowski M, Persson U. Resource use and costs in a Swedish cohort of patients with Parkinson's disease. Mov Disord 2002;17(6):1213–1220. https://doi.org/10.1002/mds.10262
14. Dodel RC, Singer M, Köhne-Volland R, et al. The economic impact of Parkinson's disease. An estimation based on a 3-month prospective analysis. Pharmacoeconomics 1998;14(3):299–312. https://doi.org/10.2165/00019053-199814030-00006
15. McCrone P, Allcock LM, Burn DJ. Predicting the cost of Parkinson's disease. Mov Disord 2007;22(6):804–812. https://doi.org/10.1002/mds.21360
16. Winter Y, Balzer-Geldsetzer M, von Campenhausen S, et al. Trends in resource utilization for Parkinson's disease in Germany. J Neurol Sci 2010;294(1–2):18–22. https://doi.org/10.1016/j.jns.2010.04.011
17. Reese JP, Winter Y, Balzer-Geldsetzer M, et al. Morbus Parkinson: Krankheitskosten einer ambulanten Patientenkohorte. Gesundheitswesen 2011;73(1):22–29. https://doi.org/10.1055/s-0030-1247571
18. Spottke AE, Reuter M, Machat O, et al. Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 2005;23(8):817–836. https://doi.org/10.2165/00019053-200523080-00007
19. von Campenhausen S, Winter Y, Rodrigues e Silva A, et al. Costs of illness and care in Parkinson's disease: an evaluation in six countries. Eur Neuropsychopharmacol 2011;21(2):180–191. https://doi.org/10.1016/j.euroneuro.2010.08.002
20. Jennum P, Zoetmulder M, Korbo L, Kjellberg J. The health-related, social, and economic consequences of parkinsonism: a controlled national study. J Neurol 2011;258(8):1497–1506. https://doi.org/10.1007/s00415-011-5969-1
21. Tamás G, Gulácsi L, Bereczki D, et al. Quality of life and costs in Parkinson's disease: a cross sectional study in Hungary. PLoS One 2014;9(9):e107704. https://doi.org/10.1371/journal.pone.0107704
22. Vossius C, Nilsen OB, Larsen JP. Parkinson's disease and nursing home placement: the economic impact of the need for care. Eur J Neurol 2009;16(2):194–200. https://doi.org/10.1111/j.1468-1331.2008.02380.x
23. Dodel RC, Eggert KM, Singer MS, Eichhorn TE, Pogarell O, Oertel WH. Costs of drug treatment in Parkinson's disease. Mov Disord 1998;13(2):249–254. https://doi.org/10.1002/mds.870130209
24. Zhao YJ, Tan LCS, Li SC, et al. Economic burden of Parkinson's disease in Singapore. Eur J Neurol 2011;18(3):519–526. https://doi.org/10.1111/j.1468-1331.2010.03210.x
25. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 1999;14(10):866–874.
26. Bach J-P, Riedel O, Klotsche J, Spottke A, Dodel R, Wittchen H-U. Impact of complications and comorbidities on treatment costs and health-related quality of life of patients with Parkinson's disease. J Neurol Sci 2012;314(1–2):41–47. https://doi.org/10.1016/j.jns.2011.11.002
27. Coelho M, Ferreira JJ. Late-stage Parkinson disease. Nat Rev Neurol 2012;8(8):435–442. https://doi.org/10.1038/nrneurol.2012.126

28. Valldeoriola F, Coronell C, Pont C, et al. Socio-demographic and clinical factors influencing the adherence to treatment in Parkinson's disease: the ADHESON study. Eur J Neurol 2011;18(7):980–987. https://doi.org/10.1111/j.1468-1331.2010.03320.x
29. Balzer-Geldsetzer M, Ferreira J, Odin P, et al. Study protocol: Care of late-stage Parkinsonism (CLaSP): a longitudinal cohort study. BMC Neurol 2018;18(1):185. https://doi.org/10.1186/s12883-018-1184-3
30. Fahn S, Elton R, Members of the UPDRS Development Committee. The unified Parkinson's disease rating scale. Recent Developments in Parkinson's Disease. Florham Park, NJ: McMellam Health Care Information; 1987:153–163.
31. Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, eds. Third Symposium on Parkinson's Disease. Edinburgh: E & S Livingston; 1969:152–157.
32. EuroQol Research Foundation 2018. EQ-5D-3L User Guide. Basic Information on How to Use the EQ-5D-3L Instrument. https://euroqol.org/wp-content/uploads/2019/10/EQ-5D-3L-User-Guide_version-6.0.pdf. Accessed Dec 18, 2019.
33. Meinshausen N. Relaxed Lasso. Comput Stat Data Anal 2007;52(1):374–393. https://doi.org/10.1016/j.csda.2006.12.019
34. Roider J, Ngoepe A, Muenchhoff M, et al. Increased regulatory T-cell activity and enhanced T-cell homeostatic signaling in slow progressing HIV-infected children. Front Immunol 2019;10:213. https://doi.org/10.3389/fimmu.2019.00213
35. Koerts J, König M, Tucha L, Tucha O. Working capacity of patients with Parkinson's disease—a systematic review. Parkinsonism Relat Disord 2016;27:9–24. https://doi.org/10.1016/j.parkreldis.2016.03.017
36. European Statistical Office. Hospital Discharges and Length of Stay Statistics. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Hospital_discharges_and_length_of_stay_statistics. Accessed Apr 28, 2021.
37. Bloem BR, Rompen L, de Vries NM, Klink A, Munneke M, Jeurissen P. ParkinsonNet: a low-cost health care innovation with a systems approach from The Netherlands. Health Aff 2017;36(11):1987–1996. https://doi.org/10.1377/hlthaff.2017.0832
38. Guttman M, Slaughter PM, Theriault M-E, DeBoer DP, Naylor CD. Burden of Parkinsonism: a population-based study. Mov Disord 2003;18(3):313–319. https://doi.org/10.1002/mds.10333
39. Guttman M, Slaughter PM, Theriault M-E, DeBoer DP, Naylor CD. Parkinsonism in Ontario: comorbidity associated with hospitalization in a large cohort. Mov Disord 2004;19(1):49–53. https://doi.org/10.1002/mds.10648
40. Das Elfte Buch Sozialgesetzbuch–Soziale Pflegeversicherung–(article 1 of the Act of 26 May 1994, BGBl. I S. 1014, 1015), as last updated by article 15 of the Act of 28 March 2021 (BGBl. I S. 591). Section 7—Pflegegeld für selbst beschaffte Pflegehilfen.
41. World Health Organization (WHO) Regional Office for Europe. Beds in Nursing and Residential Care Facilities, per 100000 Population. https://gateway.euro.who.int/en/indicators/hlthres_23-beds-in-nursing-and-residential-care-facilities-per-100-000/. Accessed Apr 27, 2021.
42. Heinzel S, Berg D, Binder S, et al. Do we need to rethink the epidemiology and healthcare utilization of Parkinson's disease in Germany? Front Neurol 2018;9:500. https://doi.org/10.3389/fneur.2018.00500
43. Hand A, Gray WK, Oates LL, et al. Medication use in people with late stage Parkinson's disease and parkinsonism living at home and in institutional care in north-east England: a balance of symptoms and side-effects? Parkinsonism Relat Disord 2016;32:120–123. https://doi.org/10.1016/j.parkreldis.2016.09.001
44. van den Berg B, Brouwer WBF, Koopmanschap MA. Economic valuation of informal care. An overview of methods and applications. Eur J Health Econ 2004;5(1):36–45. https://doi.org/10.1007/s10198-003-0189-y
45. Oliva-Moreno J, Trapero-Bertran M, Peña-Longobardo LM, Del Pozo-Rubio R. The valuation of informal care in cost-of-illness studies: a systematic review. Pharmacoeconomics 2017;35(3):331–345. https://doi.org/10.1007/s40273-016-0468-y
46. Klietz M, von Eichel H, Schnur T, et al. One year trajectory of caregiver burden in Parkinson's disease and analysis of gender-specific aspects. Brain Sci 2021;11(3):295. https://doi.org/10.3390/brainsci11030295
47. van Rumund A, Weerkamp N, Tissingh G, et al. Perspectives on Parkinson disease care in Dutch nursing homes. J Am Med Dir Assoc 2014;15(10):732–737. https://doi.org/10.1016/j.jamda.2014.05.009

Supporting Data

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