J Neurol (2011) 258:1497–1506
DOI 10.1007/s00415-011-5969-1

ORIGINAL COMMUNICATION

The health-related, social, and economic consequences of parkinsonism: a controlled national study

Poul Jennum · Marielle Zoetmulder · Lise Korbo · Jakob Kjellberg

Received: 13 November 2010 / Revised: 20 February 2011 / Accepted: 21 February 2011 / Published online: 11 March 2011

Abstract Parkinson's disease (PD) and atypical parkinsonism (AP) cause a significant socioeconomic burden, but there is insufficient information about the total disease burden at a national level. Thus, the goal of this study was to estimate the excess direct and indirect costs of PD and AP in a national sample. Using records from the Danish National Patient Registry (1997–2007), 13,400 PD and 647 AP patients were identified and compared with, respectively, 53,600 and 2,588 control cases randomly selected with respect to age, gender, civil status, and geographic location. Direct costs including frequencies of primary and sector contacts and procedures, and medication from primary and secondary sectors were obtained from the Danish Ministry of Health, the Danish Medicines Agency, and the National Health Security. Indirect costs, which included labor supply and social transfer payments, were based on income data derived from the Coherent Social Statistics. Patients with PD and AP had significantly higher rates of health-related contact and medication use and a higher socioeconomic cost. Furthermore, they had very low employment rates, and those in employment had a lower income level than employed control subjects. The annual mean excess health-related cost was €6,500 ($8,975/£5,543) and €9,771 ($13,491/£8,332) for each patient with PD and AP, respectively. In addition, the patients with PD and AP received an annual mean excess social transfer income of €324 (£276/$447) and €844 (£719/$1,165), respectively. The employment- and health-related consequences could be identified up to 8 years before the first diagnosis and increased with disease advancement. PD and AP have major socioeconomic consequences for patients and society. The health effects are present for up to more than 8 years before a diagnosis of PD/AP.

Keywords Parkinson's disease · Illness costs · Health costs · Economic burden · Employment

The study is a part of a larger database study supported by the National Board of Health and Center of Healthy Aging, Faculty of Health Sciences, University of Copenhagen with the purpose of identifying the burden of neurological diseases.

P. Jennum (✉) · M. Zoetmulder
Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Center for Healthy Aging, Faculty of Health Sciences, University of Copenhagen, Glostrup Hospital, 2600 Glostrup, Denmark
e-mail: poje@glo.regionh.dk

M. Zoetmulder · L. Korbo
Department of Neurology, Bispebjerg Hospital, 2400 NV Copenhagen, Denmark

J. Kjellberg
Danish Institute for Health Services Research, Copenhagen, Denmark

Introduction

Parkinson's disease (PD) and atypical parkinsonism (AP) are serious neurodegenerative disorders that affect a significant proportion of the adult population [1–6]. These disorders lead to a deterioration in motor, mental, and functional skills and are associated with significantly increased mortality rates, particularly for patients with AP [7]. These disorders are chronic and progressive, so PD and AP may have serious negative impacts on a patient's social life [8], family [9, 10], quality of life [11, 12], work [13, 14], and morbidity and mortality [15, 16].

Significant progress has been made in understanding the underlying pathophysiology [17–19], improving diagnostic accuracy [20], and managing these disorders [21–24]. The

pathologic disease process is characterized by progressive destruction of multiple brain regions, including the brain stem, the basic forebrain, the extra-pyramidal system, and, in later stages, almost all cerebral regions [25]. Future advances are expected to further our understanding of the brain processes underlying the disease. Great progress has also been made in developing treatment strategies, but, in spite of this, no early intervention is yet possible that reduces the severity of the disease and the associated mortality [26]. Recent studies have identified a reduced quality of life and, thus, a potential socioeconomic impact of the diseases. To date, studies on the economic impact of PD and AP have involved the use of questionnaires with selected patients, the economic burden being estimated from this information [27–32]. The identification or assumptions of costs in these studies have primarily addressed direct costs, whereas indirect costs have not been identified. As such, there has been no specific estimate of disease cost.

In Denmark, it is possible to calculate direct and indirect costs related to diseases because information from public and private hospitals and clinics in the primary and secondary sector (including medication, social, income, and employment data of all patients) is registered in central databases. It is, therefore, possible to estimate the disease effect before, during, and after diagnosis. We conducted the current national population-based study to evaluate the socioeconomic consequences of PD and AP.

Methods

In Denmark, the dates of all hospital contacts are recorded in the National Patient Registry (NPR), which also include primary and secondary diagnoses. The NPR includes administrative information, diagnoses, and diagnostic and treatment procedures using several international classification systems, including the International Classification of Disorders (ICD-10). The NPR is a time-based national database that includes data from all inpatient and outpatient contacts; therefore, the data we used are representative of all patients in Denmark who have received a diagnosis of PD or AP in the primary or secondary sector in both public and private hospitals. As all data are present throughout the observation period we can trace patients retrospectively and prospectively relative to the time of diagnosis. Furthermore, all contacts in the primary sector (general and specialist practice) and the use of medication are coded by The National Health Security and The Danish Medicine Agency, respectively. An overview of the databases is presented in Table 1 There is some underestimation of the patients with parkinsonism, as patients with contact in the primary but not the secondary sector are not coded as having the diagnosis.

Table 1 Sources of information by categories of data (Denmark)

Category of data	Sources
Case and controls	Sources
Diagnosis and year	National Patient Register
Address, age, gender, civil status	CPR Registry
Direct health costs	
The primary sector	
Consultations with general practitioners	The National Health Security System
Other practicing specialist	The National Health Security System
Drugs	The Danish Medicines Agency
The secondary sector	
Inpatient services	The Danish Ministry of Health
Outpatients and casualty ward	The Danish Ministry of Health
Indirect costs (productivity costs)	
Labor market income	Coherent Social Statistics
Social transfers	
Social transfer payments	Coherent Social Statistics
Pension	Coherent Social Statistics
Sick pay (public funded)	Coherent Social Statistics
Other public transfers	Coherent Social Statistics

All linked by national social security number

The economic consequences of PD and AP were estimated by determining the yearly cost of illness per patient diagnosed with PD (ICD DG209) and AP (ICD DG23.0–9), which includes primarily multiple system atrophy, and comparing that estimate with the cost of healthcare in a matched control group. The health cost was then divided into annual direct and indirect healthcare costs.

Direct costs included costs of hospitalization and outpatient cost weighted by use, according to diagnosis-related groups, and specific outpatient costs—all based on data from the Danish Ministry of Health. The use and costs of drugs were based on data from the National Danish Medicine Agency, which includes the retail price of the drug (and its dispensing costs) multiplied by the number of transactions. The frequencies and costs of consultations with general practitioners and other specialists were based on data from the National Health Security. Social care, nursing home care, cost of transport, etc. are not included in the (direct) cost analyses. The indirect costs, measured from the perspective of societal costs, include those related to a reduced labor supply and to social transfer payments. In Denmark, social transfer payments are income derived from state coffers. These payments include subsistence allowances, pensions, social security, social assistance, public personal support for education, and other payments. Indirect costs were based on income figures from the Coherent Social Statistics database.

Cost-of-illness studies measure the economic burden resulting from disease and illness across a defined population, including direct and indirect costs. Direct costs are the value of resources used in the treatment, care, and rehabilitation of persons with the condition under study. Indirect costs represent the value of economic resources lost because of disease-related work disability and premature mortality. As the patients leave the national data registers at the time of death, the indirect costs estimate reflects only the production loss related to disease-related work disability. It is important to distinguish costs from monetary transfer payments such as disability and welfare payments. Such payments are a transfer of purchasing power to the recipients from the general taxpayer but do not represent net increases in the use of resources and are, therefore, not included in the total cost estimate.

By reviewing the NPR, we identified all patients who received a first diagnosis of PD or AP from 1997–2007. Using data from the Civil Registration System Statistics Denmark (which contains information regarding all social information, income, pensions, etc.), we then randomly selected citizens who were of the same age and sex as the patients. Social compensation was ensured by matching control subjects with patients by civil status and by the area of the country in which they were resident. The ratio of control subjects to patients was 4:1, in order to reduce the variance among controls. Data from patients and matched control subjects that could not be identified in the Coherent Social Statistics database were excluded from the sample. More than 99% of the observations in the two groups were successfully matched. Patients and matched control subjects were followed from the year of diagnosis until 2007. If a patient or control case was not present in the CPR register on the 1st of January each year, they were not included in the dataset for that year. Patients who were not in the CPR register were typically dead, in prison, or had emigrated to another country. Costs were measured on a yearly basis and adjusted to 2005 prices using the health sector price index for health sector costs; the general price index was applied to nonmedical costs. All costs were measured in DKK and converted into Euros (€1: DKK 7.45).

The study was approved by the Danish Data Protection Agency. Data were handled in a manner that did not reveal the identity of any patient or control subject, so neither individual consent nor ethical approval was required. Statistical analysis was performed using SAS 9.1.3 (SAS, Inc., Cary, NC). Statistical significance of the cost estimates was determined for a nonparametric bootstrap analysis [33]. Since some of the samples were small or their distributions were non-normal or both, we use bootstrap to estimate the p values to attain more accurate results, than would be possible using the t test without bootstrapping. We used 100 iterations, which is sufficient for these populations.

For the large samples, the normality assumption will hold due to the central limit theorem, and the p results before and after bootstrap will be the same.

Results

In total, 13,400 patients with PD and 647 patients with AP were identified and subsequently matched with 53,600 and 2,588 control subjects, respectively. The age distribution of the patients and control subjects is shown in Table 2 As expected, the initial diagnosis of PD or AP was made in relatively old patients.

Direct costs: outpatient clinic, hospital, primary care, and drug costs

More patients than control subjects were treated in outpatient clinics, were hospitalized, and had contact with the primary care system. Compared with control subjects, more patients were taking medication and more received public support to pay for their medications (Table 3).

Indirect cost, social costs, employment rate, and income

More patients than control subjects received social services. Conversely, fewer patients with PD or AP than control subjects received income from employment (Table 3). Patients with PD or AP had lower employment rates and significantly higher social transfer rates than did control subjects. The employment rate for patients steadily decreased over time after they received a diagnosis of PD or AP, compared with the same period for control subjects

Table 2 Age and sex of patients with Parkinson's disease or atypical parkinsonism in the year of diagnosis

	Patients with PD		Patients with AP	
	%	No.	%	No.
Sex				
Men	55	7,387	56	365
Women	45	6,013	44	282
Age, years				
<20–59	8	1,019	17	107
60–69	17	2,224	29	186
70–79	38	5,151	36	236
80+	37	5,016	18	118
Total		13,400		647

Controls were matched on age and sex at the year of diagnosis; therefore, controls have the same age at sex distribution as the patients

PD Parkinson disease, *AP* atypical parkinsonism

Table 3 Percentage of patients and control receiving health services, their source of income, unemployment, transfer income, and pension or retirement for patients with Parkinson's disease and atypical parkinsonism

	Patients with PD $n = 13,400$	Control subjects $n = 53,600$	Patients with AP $n = 647$	Control subjects $n = 2,588$
Treatment location				
Ambulatory	62[a]	37	67[a]	33
In hospital	53[a]	25	53[a]	20
Medication	99[a]	89	97[a]	84
Public health insurance	99	96	99	95
Source of income				
Employment	7[a]	13	10[a]	23
Public transfer	93[a]	91	86	84
Pension[b]	81[a]	87	63[a]	75
Other public transfers	13[a]	4	24[a]	9
Sick pay (public funded)	1	1	3	2
Employed, on leave, or student	4	9	6	17
Receiving transfer income	10	3	22	5
Receiving pension benefits payable between early retirement and normal retirement pension	85	87	70	75
Other	0	0	2	2

PD Parkinson disease, *AP* atypical parkinsonism

[a] $p < 0.0001$ PD and AP patients compared to their respective control group

[b] People can receive more than 1 type of public transfer, so the sum of the transfers do not equal all public transfer income

(Table 4). A corresponding increase in social transfer expenses took place, whereas the rate of retirement was similar in both groups (not shown).

Total health costs per year

The sources of information and the average annual healthcare cost per person–year by cost categories for patients with PD or AP in Denmark, compared with age- and sex-matched control subjects, are presented in Table 4. The sum of direct net healthcare costs (general practitioner services, hospital services, and medication) and indirect costs (loss of labor market income) were €6,500 for patients with PD and €9,294 for patients with AP. Social transfer payments were all significantly higher in patients with PD or AP compared with control subjects.

Influence of age and sex on the employment and direct and indirect costs

The employment rate before and after a diagnosis has been established is shown in Fig 1 for PD and AP patients. This shows that the employment rate is affected up to 8 years before a diagnosis is assigned in PD and AP patients. Consequently, the employment, total direct and indirect costs are affected before and after the diagnosis is established, peaking at the time of diagnosis (Fig. 1, PD and AP, lower trace). This peak in costs is primarily due to increased direct costs.

The relationships of age and sex with direct and indirect costs for both men and women are shown in Fig. 2 for PD. Patients with AP show a similar pattern, which is not illustrated here. Age and sex have pronounced effects on direct costs especially with respect to higher expenses due to hospitalization and medication among younger patients. The indirect costs were significantly higher among the patients with PD/AP for all ages. The patients receive increased pension payments and have lower income levels, especially among the younger and middle-aged patients.

Discussion

Patients with PD and AP had significantly higher rates of contact with all sectors of the healthcare system: general practice, outpatient clinics, and in-hospital services. Patients had higher rates of medication use and of publicly supported payment for medication. The total expenses were higher in the group of patients with PD or AP than in age- and sex-matched control subjects. Patients with PD and AP also had lower employment rates and significantly more often received welfare payments; employed patients had lower incomes, compared with employed control subjects. The study demonstrates that PD and AP have social and

Table 4 Sources of information and the average annual health cost (in Euros) per person–year by cost categories in Denmark

Category of data	Source of information	Patients with PD $n = 13,400$	Control subjects $n = 53,600$	p Value[a]	Patients with AP $n = 647$	Control subjects $n = 2,588$	p Value[a]
Direct health costs							
Provided through the primary sector	The National Health Insurance Security System	787[b]	308	<0.001	1,061	302	<0.001
Inpatient services	Danish Ministry of Heath	4,640	1,942	<0.001	4,918	1,675	<0.001
Outpatient services	Danish Ministry of Heath	3,50	233	<0.001	456	232	<0.001
Drugs	Danish Medicines Agency	2,164	614	<0.001	1,632	562	<0.001
Total direct cost		7,941	3,097		8,067	2,771	
Labor market income	Coherent	1,328	2,984	<0.001	1,622	5,622	<0.001
Indirect cost	Social Statistics	1,655			3,998		
Sum of direct and indirect costs		9,597	3,097	<0.001	12,065	2,771	<0.001
Net yearly costs		6,500			9,294		
Social transfer payments	Coherent	10,846	10,522	<0.001	10,324	9,480	<0.001
Pension	Social Statistics	8,978	9,969	<0.001	6,628	8,444	<0.001
Other public transfers		1,764	498	<0.001	3,404	877	<0.001
Sick pay (public funded)		101	48	<0.001	261	100	<0.001

Costs were measured on a yearly basis and adjusted to 2005 prices

[a] Bootstrap, $p < 0.0001$ PD and AP patients compared to their respective control group

[b] 1 EUR correspond to 1.38 USDollar and 0.85 Great British Pound

economic consequences several years before their diagnosis is established.

The differences between patients with PD or AP and control subjects were considerable: medication costs were more than three times higher for patients with PD or AP, hospital costs were 3 times more, total healthcare costs were more than double, and the employment rate was more than 30% lower than for control subjects. Employed patients earned only two-thirds of the income of employed control subjects. Patients with PD or AP had much higher social expenditures than did control subjects. These costs are present for all ages, although they tend to be greater among the youngest patients due to increased direct costs and loss of income.

Previous studies regarding the burden of parkinsonism have focused on the direct costs, e.g., hospital services and use of treatment procedures, such as medication, surgical intervention, physiotherapy, etc. Parkinsonism significantly reduces the quality of life of patients, family members, and caregivers [12, 34–38] Several studies have documented the increased direct costs of PD using different models, e.g., quality-of-life estimates [27, 30, 39] or model estimates [40, 41], whereas others have evaluated the effect of pharmacological treatment [29, 31, 42–46] or subthalamic stimulation [28, 47–50]. Still other studies have addressed management issues related to the care of patients with AP and PD, including the effect on caregivers and families [36, 51–56] and the influence on economic and other costs. However, most of these studies have examined the economic effects of PD and AP in a limited fashion, primarily focusing on direct costs, such as reduction in the use of selected types of medication or whether subthalamic stimulation reduces the need for medication. PD and AP also have significant consequences related to work capabilities, pensions, transfer income, and other public support even though these diseases have a late onset [14, 57]; however, the importance of these factors has not previously been estimated.

The impact of PD and AP on work capabilities is considerable. As can be seen in Figs. 1 and 2, even at the time of diagnosis, patients already have significant reductions in their levels of employment. Thus, employment rate is affected before a diagnosis of PD or AP is made, with the rate falling even further after the diagnosis is confirmed. This finding has also been shown in other chronic and progressive disorders, such as narcolepsy [58]. PD and AP patients have a significant influence on social and health cost variables a long time (up to 8 years) before the diagnosis is established. The slight increase in employment rate in AP patients (Fig. 2) is due to the selection mechanism. Several factors may explain this: (1) patients may have (pre-motor?) symptoms long before PD or AP is diagnosed; (2) patients may not be able to seek a pension before they receive a diagnosis, and so remain employed before their diagnosis is made; and, (3) patients may only seek professional help when they have reached the point at which

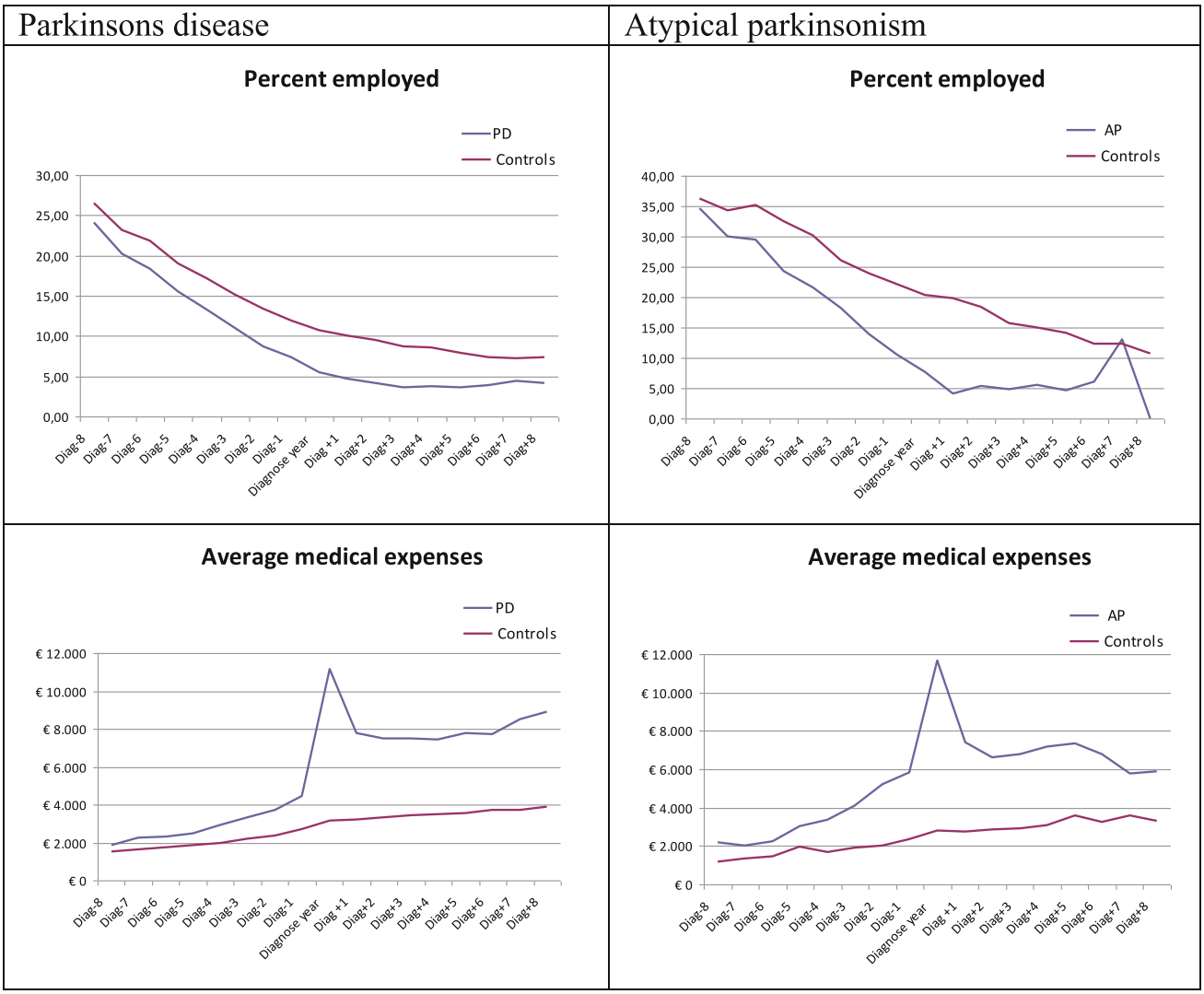

Fig. 1 The proportion of patients with a diagnosis of Parkinson's disease (PD) or atypical parkinsonism (AP) and respective control subjects who were employed before diagnosis, at diagnosis, and in follow-up years (*upper trace*). Average direct and indirect costs before, at, and after the establishment of a diagnosis of PD or AP. Eight years before and 8 years after diagnosis versus 8 years before diagnosis and any length of time after. The overall difference is significant ($p < 0.001$)

their social lives are impaired and their symptoms lead to exhaustion. Also direct costs due to hospital and health care contacts were affected up to 8 years prior to the diagnosis of PD or AP. This finding fits well with the hypothesis that the patients present symptoms and disease manifestations prior to the motor manifestations, e.g., hyposmia, urological, depressive, REM behavior disorder, which consequently leads to increased health care contacts [25]. A potential consequence of this finding is that although PD and AP may present further disease progression, the effect of the disease is already significant before and at the time of diagnosis. Disease modification intervention may affect motor skills and quality of life, but it is limited in terms of its social consequences. This may explain, in part, why many of the current treatment modalities for PD and AP have only limited effects on direct and indirect costs associated with the diseases. Consequently, if disease modification is to have an effect, earlier disease identification is important, i.e., during the pre-motor phase of disease development.

PD and AP patients tend to have one or several health contacts with the secondary sector, but patients with early or minor symptoms and contacts with the primary sector may be underestimated, as contacts in the primary sector are registered but not with a diagnosis. In general, the database represents an almost complete national patient sample. This is possible because all Danes are registered using social security codes, and data concerning health, medication, social, and employment are recorded. Therefore, all contacts with the primary and secondary sector,

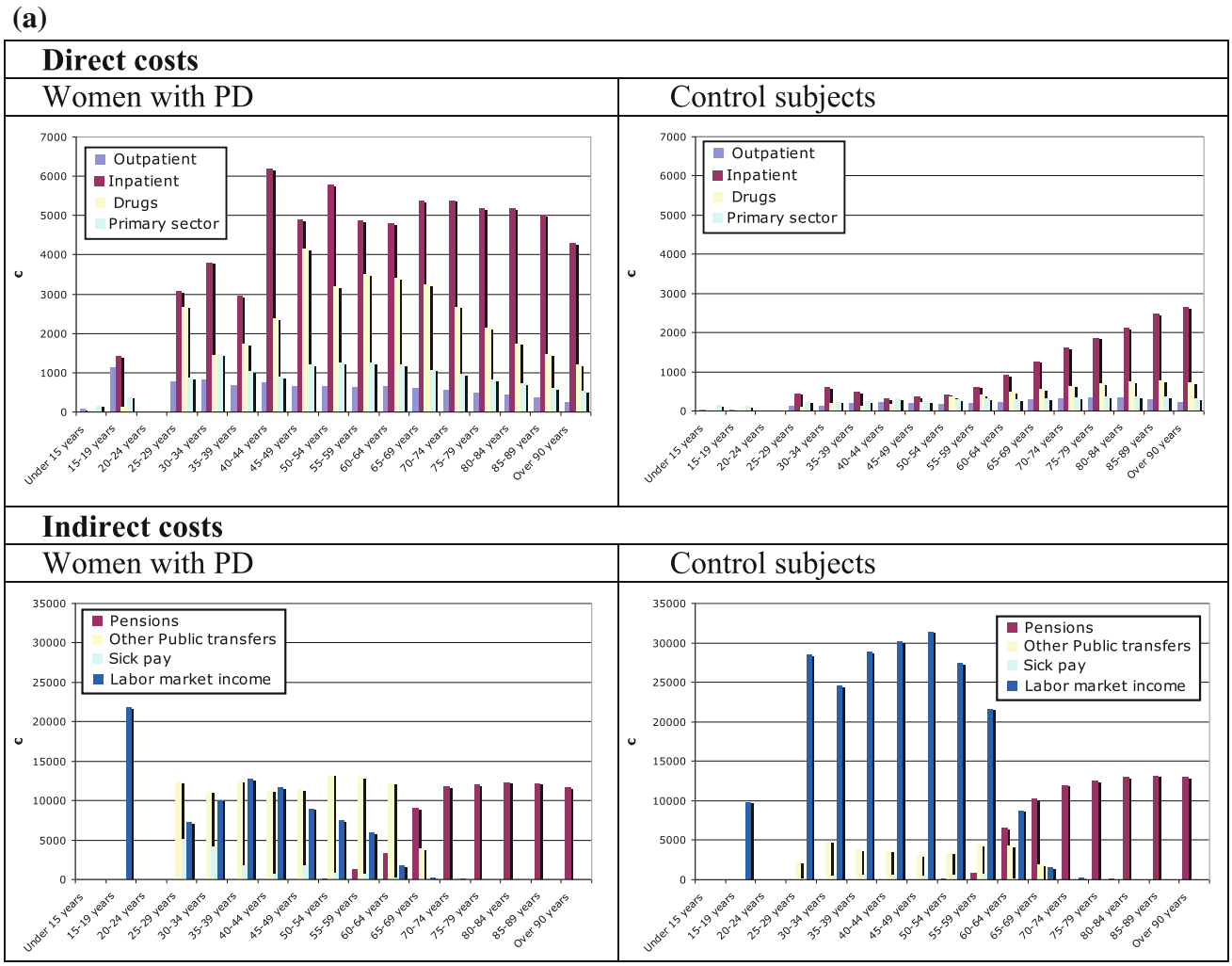

Fig. 2 Direct and indirect cost by 5-year decades for patients with a diagnosis of Parkinson's disease (PD) or atypical parkinsonism (AP). Data are presented as cost per patient. The data for females (**a**) and males (**b**), respectively, are shown. All differences are highly significant ($p < 0.001$)

including diagnostic and treatment procedures, were included in these costs. Furthermore, all indirect costs, including transfer payment costs, and income levels were included in the analysis. We did not include criteria for any other verification of the diagnoses of PD or AP, nor did we subdivide by AP type. AP represents a wide range of diagnoses with a poor prognosis. This group of disease represent a higher mortality rates, but we did not include loss of labor as this effect is smaller in the age range and difficult to estimate precisely. It is important to stress that the control group is not defined as a group of healthy subjects; they were selected on the basis of age, sex, geography, and social factors. To be included as control subjects, they could not have a diagnosis of PD or AP, but they may very well have had other disorders—the costs of which would have been included in the figures presented in Table 3. The differences observed between patients and control subjects, thus, represent those between people with PD or AP and a random population-based sample.

Consequently, the study presents the objectively determined direct and indirect costs of PD and AP that were evaluated in a national sample, compared with a control group with a similar age, sex, and social composition, over a 10-year period.

In conclusion, AP and PD lead to significantly higher health-related and social transfer costs, and lower levels of employment and income. These effects are present up to 8 years prior to the diagnosis of motor disorders indicating the significant impact of pre-motor symptoms on health and work capabilities. Appropriate treatment must be provided not only to improve quality of life, but also to assist patients in their ability to continue taking part in their family and professional lives. Additional research is needed in early disease identification, disease management,

(b)

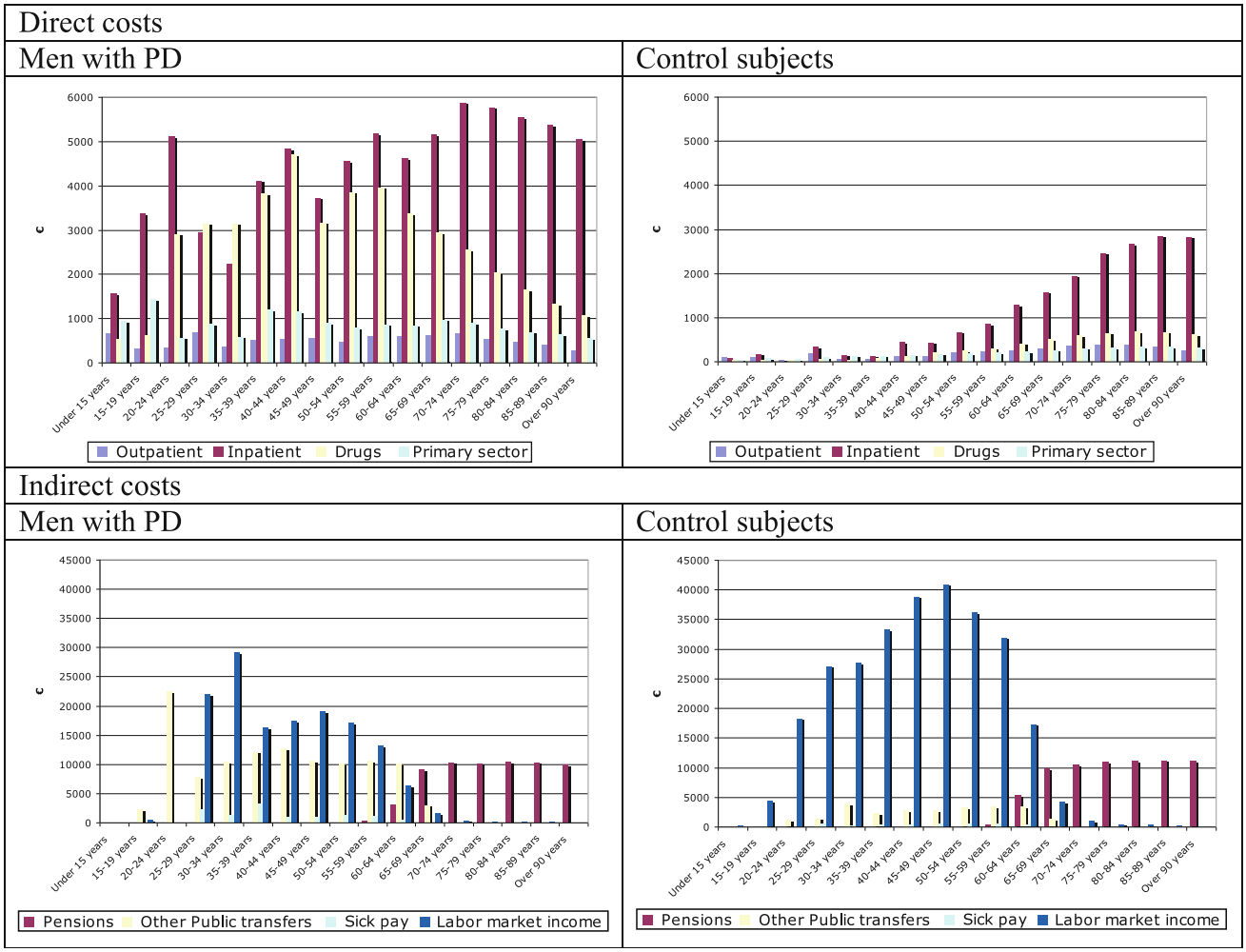

Fig. 2 continued

and the effects of PD and AP on quality of life, socio-economic factors, work capabilities, and healthcare needs so that these costs for patients and society can be reduced.

Acknowledgments The study was supported by a grant from the National Health Board.

Conflict of interests There are no conflicts of interests among the authors.

References

1. de Rijk MC, Tzourio C, Breteler MM et al (1997) Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 62:10–15
2. Wickremaratchi MM, Perera D, O'Loghlen C et al (2009) Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis. J Neurol Neurosurg Psychiatry 80:805–807
3. Yamawaki M, Kusumi M, Kowa H, Nakashima K (2009) Changes in prevalence and incidence of Parkinson's disease in Japan during a quarter of a century. Neuroepidemiology 32:263–269
4. Newman EJ, Grosset KA, Grosset DG (2009) Geographical difference in Parkinson's disease prevalence within West Scotland. Mov Disord 24:401–406
5. Pedersen KF, Larsen JP, Alves G, Aarsland D (2009) Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. Parkinsonism Relat Disord 15:295–299
6. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R (2007) How common are the "common" neurologic disorders? Neurology 68:326–337
7. Guttman M, Slaughter PM, Theriault ME, DeBoer DP, Naylor CD (2001) Parkinsonism in Ontario: increased mortality compared with controls in a large cohort study. Neurology 57:2278–2282
8. Singer E (1973) Social costs of Parkinson's disease. J Chronic Dis 26:243–254
9. McRae C, Sherry P, Roper K (1999) Stress and family functioning among caregivers of persons with Parkinson's disease. Parkinsonism Relat Disord 5:69–75
10. Caap-Ahlgren M, Dehlin O (2002) Factors of importance to the caregiver burden experienced by family caregivers of Parkinson's disease patients. Aging Clin Exp Res 14:371–377

11. Dowding CH, Shenton CL, Salek SS (2006) A review of the health-related quality of life and economic impact of Parkinson's disease. Drugs Aging 23:693–721
12. Karlsen KH, Tandberg E, Arsland D, Larsen JP (2000) Health related quality of life in Parkinson's disease: a prospective longitudinal study. J Neurol Neurosurg Psychiatry 69:584–589
13. Korchounov A, Bogomazov G (2006) Employment, medical absenteeism, and disability perception in Parkinson's disease: a pilot double-blind, randomized, placebo-controlled study of entacapone adjunctive therapy. Mov Disord 21:2220–2224
14. Schrag A, Banks P (2006) Time of loss of employment in Parkinson's disease. Mov Disord 21:1839–1843
15. Diem-Zangerl A, Seppi K, Wenning GK, Trinka E, Ransmayr G, Oberaigner W, Poewe W (2009) Mortality in Parkinson's disease: a 20 year follow-up study. Mov Disord 24:819–825
16. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G (2010) What predicts mortality in Parkinson disease? A prospective population-based long-term study. Neurology 75(14):1270–1276
17. Montgomery EB Jr (2009) Basal ganglia pathophysiology in Parkinson's disease. Ann Neurol 65:618 author reply 618–619
18. Bartels AL, Leenders KL (2009) Parkinson's disease: the syndrome, the pathogenesis and pathophysiology. Cortex 45:915–921
19. Weintraub D, Comella CL, Horn S (2008) Parkinson's disease–part 1: pathophysiology, symptoms, burden, diagnosis, and assessment. Am J Manag Care 14:S40–S48
20. Montgomery EB Jr (2006) Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 67:2266 author reply 2266
21. Olanow CW, Stern MB, Sethi K (2009) The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 72:S1–S136
22. Lang AE (2009) When and how should treatment be started in Parkinson disease? Neurology 72:S39–S43
23. Stacy M, Galbreath A (2008) Optimizing long-term therapy for Parkinson disease: levodopa, dopamine agonists, and treatment-associated dyskinesia. Clin Neuropharmacol 31:51–56
24. Stacy M, Galbreath A (2008) Optimizing long-term therapy for Parkinson disease: options for treatment-associated dyskinesia. Clin Neuropharmacol 31:120–125
25. Braak H, Rub U, Gai WP, Del Tredici K (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110:517–536
26. Hirsch EC (2007) How to improve neuroprotection in Parkinson's disease? Parkinsonism Relat Disord 13:S332–S335
27. Findley LJ (2007) The economic impact of Parkinson's disease. Parkinsonism Relat Disord 13(Suppl):S8–S12
28. Fraix V, Houeto JL, Lagrange C et al (2006) Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 77:443–449
29. Hempel AG, Wagner ML, Maaty MA, Sage JI (1998) Pharmacoeconomic analysis of using Sinemet CR over standard Sinemet in parkinsonian patients with motor fluctuations. Ann Pharmacother 32:878–883
30. Lindgren P (2004) Economic evidence in Parkinson's disease: a review. Eur J Health Econ 5(Suppl 1):S63–S66
31. Noyes K, Dick AW, Holloway RG (2004) Pramipexole v levodopa as initial treatment for Parkinson's disease: a randomized clinical-economic trial. Med Decis Making 24:472–485
32. Wang G, Cheng Q, Zheng R et al (2006) Economic burden of Parkinson's disease in a developing country: a retrospective cost analysis in Shanghai, China. Mov Disord 21:1439–1443
33. Efron B, Tibshirani RJ (1994) An introduction to the bootstrap: (monographs on statistics and applied probablity). Chapman and Hall, London
34. Goldsworthy B, Knowles S (2008) Caregiving for Parkinson's disease patients: an exploration of a stress-appraisal model for quality of life and burden. J Gerontol B Psychol Sci Soc Sci 63:P372–P376
35. Kim KS, Kim BJ, Kim KH et al (2007) Subjective and objective caregiver burden in Parkinson's disease. Taehan Kanho Hakhoe Chi 37:242–248
36. Martinez-Martin P, Arroyo S, Rojo-Abuin JM, Rodriguez-Blazquez C, Frades B, de Pedro Cuesta J (2008) Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. Mov Disord 23:1673–1680
37. Martinez-Martin P, Benito-Leon J, Alonso F et al (2005) Quality of life of caregivers in Parkinson's disease. Qual Life Res 14:463–472
38. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M (2006) Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord 12:35–41
39. Spottke AE, Reuter M, Machat O et al (2005) Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 23:817–836
40. Coyle D, Oakley J (2008) Estimating the expected value of partial perfect information: a review of methods. Eur J Health Econ 9:251–259
41. Noyes K, Liu H, Temkin-Greener H (2006) Cost of caring for Medicare beneficiaries with Parkinson's disease: impact of the CMS-HCC risk-adjustment model. Dis Manag 9:339–348
42. Bryson HM, Milne RJ, Chrisp P (1992) Selegiline: an appraisal of the basis of its pharmacoeconomic and quality-of-life benefits in Parkinson's disease. Pharmacoeconomics 2:118–136
43. Hudry J, Rinne JO, Keranen T, Eckert L, Cochran JM (2006) Cost-utility model of rasagiline in the treatment of advanced Parkinson's disease in Finland. Ann Pharmacother 40:651–657
44. Iskedjian M, Einarson TR (2003) Cost analysis of ropinirole versus levodopa in the treatment of Parkinson's disease. Pharmacoeconomics 21:115–127
45. Noyes K, Dick AW, Holloway RG (2007) The implications of using US-specific EQ-5D preference weights for cost-effectiveness evaluation. Med Decis Making 27:327–334
46. Palmer CS, Nuijten MJ, Schmier JK, Subedi P, Snyder EH (2002) Cost effectiveness of treatment of Parkinson's disease with entacapone in the United States. Pharmacoeconomics 20:617–628
47. Charles PD, Padaliya BB, Newman WJ et al (2004) Deep brain stimulation of the subthalamic nucleus reduces antiparkinsonian medication costs. Parkinsonism Relat Disord 10:475–479
48. McIntosh E, Gray A, Aziz T (2003) Estimating the costs of surgical innovations: the case for subthalamic nucleus stimulation in the treatment of advanced Parkinson's disease. Mov Disord 18:993–999
49. Spottke EA, Volkmann J, Lorenz D et al (2002) Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. J Neurol 249:759–766
50. Valldeoriola F, Morsi O, Tolosa E, Rumia J, Marti MJ, Martinez-Martin P (2007) Prospective comparative study on cost-effectiveness of subthalamic stimulation and best medical treatment in advanced Parkinson's disease. Mov Disord 22:2183–2191
51. Berry RA, Murphy JF (1995) Well-being of caregivers of spouses with Parkinson's disease. Clin Nurs Res 4:373–386
52. Edwards NE, Ruettiger KM (2002) The influence of caregiver burden on patients' management of Parkinson's disease: implications for rehabilitation nursing. Rehabil Nurs 27:182–186, 198

53. Happe S, Berger K (2002) The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing 31(5):349–354
54. Reese SL (2007) Psychosocial factors in Parkinson's disease. Dis Mon 53:291–295
55. Teel CS, Press AN (1999) Fatigue among elders in caregiving and noncaregiving roles. West J Nurs Res 21:498–514; discussion 514–420
56. Vossius C, Nilsen OB, Larsen JP (2009) Parkinson's disease and nursing home placement: the economic impact of the need for care. Eur J Neurol 16:194–200
57. Martikainen KK, Luukkaala TH, Marttila RJ (2006) Parkinson's disease and working capacity. Mov Disord 21:2187–2191
58. Jennum P, Knudsen S, Kjeldberg J (2009) The economic consequences of narcolepsy. J Clin Sleep Med 5:240–245