J Neurol (2008) 255 [Suppl 5]:18–32
DOI 10.1007/s00415-008-5004-3

Epidemiology of Parkinson's disease

Guido Alves
Elin Bjelland Forsaa
Kenn Freddy Pedersen
Michaela Dreetz Gjerstad
Jan Petter Larsen

G. Alves, MD, PhD (✉) ·
E. B. Forsaa, MD · K. F. Pedersen, MD ·
M. Dreetz Gjerstad, MD, PhD ·
J. P. Larsen, MD, PhD
The Norwegian Centre for Movement Disorders
Stavanger University Hospital
PO 8100
4068 Stavanger, Norway
Tel.: +47-5151/5603
Fax: +47-5151/5515
E-Mail: algu@sus.no

J. P. Larsen, MD, PhD
Institute of Clinical Medicine
School of Medicine
University of Bergen
PO 7800
5020 Bergen, Norway

G. Alves, MD, PhD · E. B. Forsaa, MD ·
K. F. Pedersen, MD · M. Dreetz Gjerstad, MD, PhD · J. P. Larsen, MD, PhD
Dept. of Neurology
Stavanger University Hospital
PO 8100
4068 Stavanger, Norway

Abstract Epidemiological research aims to provide information on the development, prevalence and progression of diseases, and their associated risk factors. Epidemiological research is thus the basis of increasing our understanding on the aetiology of diseases and as a consequence the starting point for identifying at risk groups in the population, development for novel prevention and treatment strategies, and health care planning. This review provides an overview of the epidemiology of Parkinson's disease, the second most common neurodegenerative disorder, with special emphasis on population-based data on the clinical progression of motor and non-motor features of the disease.

Key words Parkinson's disease · epidemiology · population-based · progression

Introduction

Parkinson's disease (PD) is the most common movement disorder besides essential tremor and the second most common neurodegenerative disease [156]. PD is neuropathologically characterized by nigrostriatal cell loss and presence of intracellular α-synuclein-positive inclusions called Lewy bodies. Originally understood as a dopamine-deficit disorder, increasing evidence suggests PD to be a multi-system brain disease in which various non-dopaminergic transmitter systems are affected at motor onset and become more prominent during the course of the disease [123]. Recently, Braak and coworkers proposed a staging procedure of PD pathology from stage 1 to 6 [19, 20]. This staging procedure suggests a premotor period in which typical pathological changes, Lewy neurites and Lewy bodies, spread from the olfactory bulb and vagus nerve to lower brainstem regions (medulla oblongata and pontine tegmentum) (stages 1 to 2), followed by a symptomatic period when pathological changes involve the midbrain including substantia nigra (stage 3), mesocortex (stage 4) and eventually neocortex (stages 5 to 6). Whether the premotor period in PD is long-lasting or begins in rather close temporal relation to the clinical onset is the subject of debate [63].

When PD becomes clinically overt, tremor, rigidity, bradykinesia, and postural instability are considered to be the cardinal signs of the disease. The course of the disease is chronic and progressive, and may be complicated by a wide range of motor and non-motor features, many of which contribute to increased disability as well as diminished quality of life in patients and caregivers [141]. However, there is a remarkable interindividual heterogeneity in the course of PD.

In this review, we provide an overview of current knowledge on epidemiological aspects of PD, with special focus on population-based data on the clinical progression of motor and non-motor features.

JON 5004

Diagnosis of PD in epidemiological research

A definite diagnosis of PD requires post-mortem confirmation. Although structural and functional neuroimaging may be useful in the differential diagnosis of PD and related disorders [137,142] and is more or less frequently used in everyday practice, the diagnosis of PD in epidemiological research usually relies on clinical criteria which, at best, provide a diagnosis of probable PD. In many epidemiological studies, PD is diagnosed based on the *unequivocal* presence of at least two of the four motor cardinal signs and the absence of atypical features such as severe postural instability and frequent falls, autonomic, pyramidal or cerebellar features, eye movement disorders, or lack of response to dopaminergic treatment. Diagnosing PD and related disorders at a sufficient level of accuracy, however, may be a challenge, particularly during the early stages of the disease when there is no information on levodopa-responsiveness and atypical features may be absent or mild. Clinicopathological studies in selected patient cohorts with autopsy-proven diagnosis report the clinical diagnosis to be changed during life in more than 1/3 of those initially diagnosed with PD and in 60 % of subjects with other parkinsonian syndromes [68]. Therefore, more restrictive operationalized sets of diagnostic criteria have been developed. The most frequently used research criteria are those of the UK Parkinson's Disease Society Brain Bank (UKBB) [67] and the National Institute of Neurological Disorders and Stroke (NINDS) [46]. When these criteria are applied by movement disorders specialists, about 90 % of cases are diagnosed correctly [68]. However, there is little information on reliability and validity of these criteria when applied early during the course of the disease and by general neurologists.

Differential diagnosis

Parkinsonian features may be subtle at the onset of the disease, and misdiagnosis is therefore not uncommon. In a community-based study, only 53 % of patients on antiparkinsonian drugs initiated by general practitioners due to suspected PD fulfilled UKBB criteria of probable PD when investigated by neurologists [104]. The most common misdiagnoses were essential tremor, vascular parkinsonism and Alzheimer's disease (AD). Clinical features that may help to distinguish PD from other parkinsonian disorders are asymmetry of motor symptoms, tremor at rest, and good/ excellent response to levodopa treatment [94]. However, none of these features definitively differentiates PD from other parkinsonian disorders. For example, asymmetry of motor features is typically seen in corticobasal degeneration, while "good" or "excellent" initial levodopa response was absent in about one of five patients with pathologically proven PD [69]. Severe autonomic dysfunction, gaze palsy, and gait dysfunction at disease onset are uncommon and suggest atypical parkinsonian disorders like multiple system atrophy (MSA) or progressive supranuclear palsy (PSP). Lower body parkinsonism associated with gait apraxia is also frequently seen in vascular parkinsonism. According to current consensus criteria [103], a diagnosis of dementia with Lewy bodies (DLB) should be provided in patients developing dementia within one year after motor onset, particularly in those with hallucinations, fluctuating attention, and other early clinical signs of visuospatial or executive dysfunction. Parkinsonian features also occur in a considerable portion of patients with Alzheimer's disease (AD) and other dementia disorders. For a more detailed overview see Table 1.

Prevalence and incidence of PD

Methodological differences between studies make direct comparison of prevalence and incidence estimates difficult. The disease is found in all ethnic groups, but with geographical differences in prevalence. Early onset of sporadic PD is rare, with about 4 % of patients developing clinical signs of the disease before an age of 50 years [164]. Approximately 1–2 % of the population over 65 years suffers from PD. This figure increases to 3 % to 5 % in people 85 years and older [33]. As PD is mainly an illness of later life, it is more common in developed countries were people live longer. Most community-based prevalence studies across Europe found crude prevalence rates between 100 and 200 per 100,000 inhabitants [168]. Incidence calculations are thought to be a more precise estimate of the frequency of the disease as they

Table 1 Differential diagnosis in parkinsonian disorders

Type of parkinsonism	Subtype/cause
Parkinson's disease[a]	• Idiopathic • Familial
Symptomatic parkinsonism	• Drug-induced ○ Neuroleptics, antidepressants, lithium ○ Antiemetics ○ Antihypertensive agents, antiarrhythmics • Vascular disease • Intoxication (MPTP, rotenone, others) • Traumatic • Post-infectious • Neoplasm • Normal pressure hydrocephalus
Parkinsonism due to other neurodegenerative disorders	• Atypical parkinsonism ○ Multiple system atrophy (MSA)[a] ○ Progressive supranuclear palsy (PSP)[b] ○ Corticobasal degeneration (CBD)[b] • Dementia with Lewy bodies (DLB)[a] • Alzheimer's disease[b] • Others

[a] synucleinopathy; [b] tauopathy

are not influenced by mortality. However, there are substantial variations in reported incidence rates, most probably due to methodological differences between studies, in particular differences in case ascertainment and use of diagnostic criteria. Age-standardized incidence rates of PD in population-based studies in European countries and the USA range from 8.6 to 19.0 per 100,000 inhabitants when strict diagnostic criteria of PD are applied [161]. As may be anticipated, door-to-door surveys and studies using broader inclusion criteria have yielded higher prevalence and incidence figures [161, 168].

Risk factors for developing PD

The etiology of PD remains unclear in the majority of cases. Current theories suggest a combination of age, genetic and non-genetic factors to be involved in PD etiology [4].

Genetic risk factors

Family members of affected patients are at 3- to 4-fold increased risk to develop the disease compared to subjects in the general population or controls [11, 85]. Due to this aggregation of PD within families and pedigrees, a genetic cause of the disease has been hypothesized for several decades. During the last decade, several gene loci were found to be associated with autosomal-dominantly [45, 89, 121, 173] or recessively [81, 163, 165] inherited parkinsonism. Most of the so far known gene mutations cause juvenile or early onset of the disease, while others such as the most recently identified *leucine-rich repeat kinase 2* (*LRRK2*) mutations appear to cause parkinsonism resembling sporadic PD with respect to both clinical and demographical features [57, 182]. The discovery of these genetic mutations and the increased understanding of dysfunction of their aberrantly encoded proteins have provided important and novel insights into the molecular pathogenesis of the disease. There is now compelling evidence that impairment of the ubiquitine-proteasome system, mitochondrial dysfunction and decreased oxidative stress tolerance are key pathologic mechanisms in PD pathogenesis [32, 41]. However, the exact mechanisms are not completely understood [118], and monogenetic causes only account for a small proportion (< 10 %) of all PD cases, while the vast majority of PD cases appear to be sporadic. In these, occupational, lifestyle and environmental factors, possibly in interaction with each other or with susceptibility genes, may play a part.

Non-genetic risk factors

A large variety of putative environmental, occupational and life-style risk factors for PD have been investigated during recent decades. For many risk factors, studies have shown inconsistent or contradictory results [31, 86]. Results from these studies have to be interpreted in the light of several kinds of potential bias, particularly recall bias in retrospective studies, but also reversed causality, as there is uncertainty regarding the duration of the pre-motor period in which the underlying disease process has already started but not become clinically overt. Most consistently, exposure to pesticides and cigarette smoking has been linked to a higher and lower risk, respectively, for developing PD. For more detailed reviews of this topic see [31, 86].

Gender and PD risk

Gender differences in the risk of developing PD have been described in numerous studies, most of them reporting higher incidence rates in males, particularly in the oldest age groups [157]. Several studies found no differences in incidence of PD between men and women aged less than 60 years at onset. Neuroprotective properties of female steroid hormones, or alternatively gender differences in exposure to environmental and occupational risk factors or gender-specific genetic influences have been discussed as possible underlying causes [144, 157]. In a recent meta-analysis of 17 incidence studies [157], the overall age-adjusted male to female (M:F) ratio for incident PD was 1.46. However, gender differences in incidence of PD appear to differ by ethnicity. Among 14 studies conducted in Western populations, the M:F ratio was 1.58 and only two studies found a M:F ratio of lower than 1, while in Asian populations gender distribution was almost equal (M:F ratio 0.95).

Premotor features

Non-motor features found to be associated with higher risk of PD in the general population, frequently suggested to be premotor symptoms of the disease, include constipation, olfactory dysfunction, depression/anxiety and REM sleep behavior disorder (RBD). These are more thoroughly discussed by others [160] and in part below.

Progression of motor symptoms and disability

Due to lack of in vivo biomarkers and the current limitations of functional neuroimaging methods as surrogate markers of disease progression in PD [109], clinical

assessment using established clinical rating scales remains the gold standard in charting the course of the disease.

Rating scales

Various clinical instruments have been used for evaluation of motor severity and disability in patients with PD, although many of them have not been sufficiently evaluated for reliability and validity [129]. The most widely used and accepted rating tool in PD is the Unified Parkinson's Disease Rating Scale (UPDRS), which was introduced in 1987 by an international group of movement disorders specialists [34]. The UPDRS was designed to follow the longitudinal course of the disease and has been shown to be both reliable and valid [129]. It is divided into four parts (subscales), covering symptoms of mentation, behavior, and mood in part I, activities of daily living in part II, motor symptoms in part III, and complications of therapy in part IV. Each item in part I and III is quantitatively scored on a 5-point scale (from 0 to 4). Despite its strengths, the UPDRS is currently under revision to adapt it to recent scientific advances, particularly to better capture the wide spectrum of non-motor problems experienced by patients with PD. The Hoehn and Yahr scale was devised in 1967 and is the other main scale used in PD [64]. It measures the stage of the disease by including both impairment and disability of movements, balance, and gait. The scale is allocating stages from 0 (no signs of disease) to 5 (wheelchair bound or bedridden unless assisted). Non-motor features are, however, not captured by the Hoehn and Yahr scale.

Cardinal signs

Tremor at rest (4–6 Hz frequency) is the most common cardinal sign at motor onset [70, 75, 139]. However, 25 % of patients with PD never develop tremor [70]. Rest tremor in PD is usually a supination-pronation tremor, asymmetric, and most prominent in the distal part of an extremity, lost during sleep, reduced in action, and worsened by excitement, anxiety, or apprehension. *Bradykinesia,* referring to slowness of movements with difficulties in initiating and maintaining motions, and *rigidity,* characterized by increased resistance to passive stretch of skeletal muscles, are less common than rest tremor but are still frequently seen at onset of PD.

Axial symptoms, including postural instability and impairment of speech, are not typical at disease onset, but become a common complication of advanced PD. In a community-based study of 128 patients with PD, 64 % had postural instability with falls and 49 % had speech difficulties at an average of six years of disease duration. Only 1 % of these patients reported unsteadiness as their initial symptom [138]. In a prospective population-based longitudinal study of patients who were non-demented at baseline, the proportion of patients with predominant postural instability and gait difficulties (PIGD) increased from 53.8 % to 88.1 % during 8 years of follow-up [8]. Prospective clinic-based studies of falls in PD found that nearly 70 % of patients with PD fall at least once each year [54]. In a prospective long-term study, 81 % of patients had fallen due to the disease after 15 years of follow-up [60]. Similar to this, a retrospective study of 474 patients with pathologically proven PD reported that 73.3 % had fallen during the course of the disease, 16.9 % had suffered bone fractures, and the average time from onset to the first fall was 9 years [171]. In this study, female gender, older age, symmetrical onset and autonomic dysfunction each independently predicted earlier falls. In a meta-analysis of prospective studies of falling in PD, the strongest predictor of falling was prior falls in the preceding year, while disease severity itself was a poor predictor of falls [124].

In the very majority of patients with PD, the initial motor symptoms are localized to the upper extremities [162], spread to the other ipsilateral limb within one to three years, and affect the contralateral limbs in three to eight years [126]. The asymmetrical pattern, however, usually persists during the course of the disease, even in advanced stages [71]. Severity of bradykinesia, rigidity, and gait and balance progress similarly, while tremor severity appears to be rather stable over time, possibly indicating different underlying pathophysiological processes [97].

Freezing of gait

Freezing of gait (FOG) is a gait disorder in which patients are unable to initiate or continue locomotion and is an important source of falls [149]. FOG describes the patients' difficulty to move their feet and may become apparent as start hesitation, turn hesitation, destination hesitation, or halting when walking. FOG often occurs suddenly, may be triggered by visual stimuli like narrow spaces and doors, is usually transient, and predominantly appears in off-state. Frequency and severity of FOG increases with the progression of PD. Severe FOG in the early stage are atypical for PD and suggests other diagnoses such as pure freezing syndrome or PSP. In the DATATOP trial, 7 % of patients with mild PD reported FOG before treatment was initiated [47]. 26 % of patients experienced FOG at the end of the study [47]. Baseline risk factors for development of FOG in this study were absence of tremor and longer disease duration. The pathophysiological basis of this phenomenon is poorly understood, but a strong association with development of axial symptoms may indicate common underlying pathology [47].

Rate of functional decline

Although the nature of PD is usually described as slowly progressive, rather few prospective studies have provided estimates on the rate of functional decline in PD using currently acknowledged clinical rating scales, such as the UPDRS and the Hoehn and Yahr scale. Drug trials including placebo arms provide information on the natural progression of motor symptoms in patients with early disease, estimating the rate of progression in drug-naïve PD patients to be 3.6 to 13.4 points per year, as measured by the UPDRS motor score [1, 158]. Similar progression rates have been found in neuroimaging studies, reporting progressive degeneration in the striatum of 4 % to 13 % per year in PD [63, 110]. The rate of motor decline is less rapid in drug-treated patients. Two population-based longitudinal cohort studies found annual progression rates in the UPDRS motor score of 1.5 % and 3.1 % of the maximum score [10, 97]. Similar rates were reported from another community-based sample using self-administered Hoehn and Yahr scales to assess disease progression [140]. Several studies in early PD suggest that on average five years after initiation of drug therapy severity of motor impairment and disability have returned to levels found before treatment was started [44, 82].

Information on the natural long-term disease progression in PD comes from studies conducted in the pre-levodopa era, but is limited. In a study by Mjønes, 40 % of patients developed impairment of work ability within the first four years of disease duration [107]. Hoehn and Yahr, in their classic article, reported that 37 % of patients with PD had reached stage III or above within four years of disease duration, while 34 % of those with a disease duration for ten years or more still were in stage I or II [65]. More recent studies suggest that the rate of functional decline is similar in treated patients. Müller et al. studied retrospectively the progression of Hoehn and Yahr stages in a selected cohort of patients with pathologically confirmed PD and found no patient with progression to Hoehn and Yahr stage III within the first year of motor onset [112]. In the same study, median duration from debut to Hoehn and Yahr stage II and III was 3 years and 5.5 years, respectively, similar to the results published by Hoehn and Yahr. In a prospective long-term study following treated PD patients for 15 years, the average Hoehn and Yahr stage was 3.8 in on-state and 4.1 in off-state [60]. In this study, the authors also compared data on the Hoehn and Yahr staging in their patients with those from the pre-levodopa study by Hoehn and Yahr and found no differences in long-term results. They concluded that modern treatment does not lead to significant long-term benefit in patients with PD.

There is a remarkable interindividual variation in the progression of PD, which has resulted in numerous studies investigating predictors of more or less rapid functional decline in PD. During recent years, three reviews have attempted to summarize evidence on predictors of functional decline in PD [102, 128, 150]. Methodological weaknesses were observed in most studies, leading to limited or inconsistent results on several potential risk factors of functional decline. Evidence from prospective long-term studies suggests that higher age at motor onset is the major denominator of more rapid motor progression in PD [10, 59]. In one of these studies [10], the annual increase in UPDRS motor score was shown to be about 1.5 times more rapid in patients aged 70 years at motor onset compared to subjects aged 50 years at onset. The predicted time for progressing one Hoehn and Yahr stage for patients aged 70 years and 50 years at motor onset was 5.1 years and 9.3 years, respectively. Less consistently identified risk factors for more rapid functional decline in PD were a PIGD motor subtype, lack of rest tremor, more severe functional impairment, and cognitive dysfunction [102, 128, 150]. Whether the duration of the disease has impact on functional decline is a matter of debate, some studies suggesting a non-linear progression of motor symptoms with more rapid decline during the early stages of the disease [140]. Interestingly, several features discussed to influence the risk for developing PD, such as cigarette smoking, coffee and tea consumption, and pesticide exposure appear not to impact the rate of motor progression in overt PD [7, 53, 77].

Motor complications

The course of PD is frequently complicated by variations in motor response. Motor complications comprise dyskinesias, which are episodes of abnormal involuntary movements involving head, trunk, and limbs, and motor fluctuations, describing a transient decline in motor performance. The presence and development of dyskinesias and motor fluctuations are associated with each other [58] and both features increase in frequency and severity with the duration of the disease [13].

In clinic-based studies, approximately 40 % of patients developed motor problems within four to six years after disease onset [3]. In a long-term study, dyskinesias and "end of dose failure" had been experienced by about 95 % of subjects at 17 years of disease duration [60]. However, these may be overestimates of the frequency of motor complications due to selection bias. Population-based studies found lower prevalence rates of motor complications in PD [87, 138]. In a community-based study, 78 % of the patients did not experience motor fluctuations after more than 6 years of levodopa treatment [87]. In another population-based study from England, 28 % of levodopa-treated patients suffered from dyskinesias and 40 % from response fluctuations after about seven years of disease duration [138]. The risk of

developing motor complications has been attributed to younger age of onset, increased disease severity, and higher daily levodopa dose [13].

Progression of non-motor symptoms

The vast majority of patients with PD will experience non-motor problems during the course of their disease. In a cross-sectional clinic-based study of 99 patients with PD, only 12 % had no non-motor problems after seven years of disease duration [145]. Sleep disturbances, autonomic dysfunction, olfactory deficits, sensory complaints, and in particular a wide range of neuropsychiatric problems including cognitive impairment may lead to substantially reduced functioning and quality of life [141].

Cognitive impairment and dementia

Cognitive impairment may be present even in the early stages of PD. In a community-based survey in early PD, 36 % of the patients had evidence of cognitive impairment at diagnosis [39]. At a mean of 3.5 years from diagnosis, 10 % of patients had developed dementia and further 57 % showed evidence of cognitive impairment [170]. This is in line with findings in a community-based prevalence study in which more than half of non-demented patients had some form of cognitive impairment [76]. The cognitive profile in patients with the disease varies somewhat, but executive impairment, including working memory and attention shift, and visuospatial dysfunction characterize early cognitive impairment in PD [29].

The cognitive impairment in patients with PD is progressive. The mean annual decline on the MMSE in a population-based prevalence sample of 129 patients with PD was found to be one point [177]. However, while the change in score for non-demented patients was small, patients with dementia declined with 2.4 points per year [177]. With advance in PD, there is an increase in the severity and range of cognitive deficits, probably reflecting the involvement of cortical structures. Performance on tests of orientation and attention best differentiate dementia associated with PD (PDD) from AD [18]. In community-based studies using standardized cognitive assessment and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IIIR criteria, prevalence rates of dementia range from 18 % to 41 % [132]. However, as dementia is associated with increased mortality [92], cross-sectional studies are likely to underestimate the true frequency of PDD. Prospective follow-up of an Australian cohort revealed that 17 years after disease onset, only 15 % of surviving subjects were not cognitively impaired [60]. In a prospective population-based survey of 224 patients with PD, the cumulative prevalence of dementia after 17 years of disease duration was 78 % [175]. The risk for developing dementia is up to 6-fold higher in PD than in non-PD subjects [176], and about 10 % of patients with PD develop dementia per year [99, 176]. The cumulative incidence of dementia steadily increases with age and duration of PD and, conditional on survival, increases to 80 % to 90 % by age 90 years [22]. Overall, about 3–4 % of patients with dementia have PDD [169].

Prospective studies indicate that advanced age rather than higher age at onset is a risk factor for PDD [72, 90, 175, 178]. Other factors that are independently associated with increased risk for incident dementia in PD are mild cognitive impairment and severity of parkinsonism, particularly axial symptoms like postural instability and speech problems [8, 72, 90, 91, 175]. During 8-year prospective follow-up of a community-based prevalence sample of non-demented patients with PD, development of PIGD parkinsonism was strongly associated with more rapid cognitive decline and an about 50 % risk for dementia within the following 4 years [8]. This figure corresponds well to that of another longitudinal study, reporting that 25 % of subjects with a PIGD motor subtype developed dementia over two years [21]. In both studies, none with tremor-dominant PD were demented.

Other neurobehavioral disturbances

Neuropsychiatric problems are common in PD. In a population-based study of 139 patients with PD, 61 % suffered from at least one neuropsychiatric symptom after 12 years of disease duration [180]. Of importance, charting the frequency of cognitive impairment, dementia, and fatigue was not part of this investigation. The most common behaviors found were depression (38 %) and hallucinations (27 %).

Psychotic symptoms in PD (PDPsy) include illusions, the sense of presence, simple and complex hallucinations with and without insight, and delusions. Visual hallucinations are found to be the most common form, while auditory, olfactory and tactile hallucinations are less frequent and usually present together with visual hallucinations [27, 37, 52]. Provisional diagnostic criteria for PDPsy have recently been published [130]. PDPsy in patients with PD rarely occurred before the introduction of dopaminergic treatment [36, 73]. Dopaminergic agents are therefore understood as an important cause to psychotic symptoms and abnormal behavior in PD. However, in several prospective studies no association between hallucinations and dosages of dopaminergic agents or treatment duration was found [66, 179]. In contrast, other factors such as advancing age, disease duration and severity, sleep and visual disorders, and most

consistently cognitive impairment were identified as risk factors for hallucinations in patients with PD [35, 73]. Due to the latter observation, a current theory is that hallucinations are due to a combination of dopaminergic (over-)stimulation and more widespread cerebral involvement [35]. Thus, an increase in frequency is expected as the disease progresses. Reported prevalence rates of hallucinations vary, most likely due to differences in patient selection and study design, and range from 16 % to 75 % in prospective cross-sectional studies [73]. In a population-based study from England, 18.5 % of 124 patients with PD suffered from hallucinations after 6 years of disease duration [138], compared to 26.6 % of patients with a mean disease duration of 12 years in a Norwegian cohort [179]. Longitudinal studies of hallucinations in PD are rare. In a prospective clinic-based survey of 89 PD patients with a mean disease duration of about 10 years at baseline, hallucinations were progressive and persistent, affecting 33 % at study entry and 63 % of patients four years later [52]. Hallucinations are one of the main features causing hospitalization and nursing home placement in patients with PD [181].

Depressive symptoms are significantly more common in PD than in age-matched controls and patients with other chronic diseases [114, 154]. Depressive symptoms may occur many years before the motor onset of PD [143]. About 20 % of patients report depressive symptoms before diagnosis, and the risk for developing PD is 2–3 fold increased in depressed patients compared to non-depressed control subjects [88, 114, 115]. In a recent systematic review of prevalence studies of depression in PD, frequency rates ranged from 12.7 % to about 90 % in clinic-based studies and from 2.7 % to 35 % in population-based surveys fulfilling quality criteria for inclusion [131]. This variation is likely to be the result of methodological differences between studies in the studies included. The weighted prevalence of major depression, minor depression and dysthymia was 17 %, 22 % and 13 %, respectively [131]. Thus, in the majority of patients depressive symptoms are of mild to moderate severity. In those with dementia, however, the portion of patients suffering from major depression is substantially higher [155]. Despite the high frequency of depressive symptoms in PD, suicide is not more common in patients with the disease compared to the general population [113, 148]. The association between depression and various disease-related features have been studied over the years. Disability, disease severity, axial involvement, cognitive impairment and left hemisphere involvement were found to correlate with depression in PD in the majority of studies, while results were more inconsistent regarding age at onset, female gender and previous depressive episodes [167].

Apathy is commonly used to refer to a state of diminished motivation and is characterized by simultaneous reduction in goal-directed motor, emotional and cognitive activity, such as lack of initiative and effort to perform everyday activities, flattening of affect or lack of emotional responses, and lack of intellectual interest and initiative regarding personal, social, or occupational issues [100]. Symptoms of apathy may overlap with those of depression, but there is evidence that these conditions are separable from each other [74, 93]. There is a lack of longitudinal studies of apathy in PD, and thus there is an uncertainty whether and how characteristics of apathy may change over time. Observed frequency rates of apathy vary substantially, ranging from 17 % to 70 % [174]. This variation has been attributed to use of different rating scales of apathy, different cut-off values, and other methodological differences [174]. In the so far largest and only population-based study of apathy in PD, 16.5 % were diagnosed with apathy after 12.6 years of disease duration [180]. In several cross-sectional studies apathy severity/frequency correlated with cognitive impairment and dementia, and in particular executive dysfunction [74, 93, 125]. Thus, in those with advanced PD higher prevalence rates of apathy are expected compared to patients with early disease.

Fatigue is a subjective experience that can be defined as an overwhelming sense of tiredness, lack of energy, or feeling of exhaustion. It is frequently seen in the general population, both in developing and developed countries [122], but is significantly more prominent in several neurologic, psychiatric and systemic diseases [23, 24]. Fatigue in PD may occur as a physical or mental problem, and both dimensions of fatigue are more prominent in PD compared to age-matched control, but are not correlated with each other [96]. As with other non-motor symptoms, fatigue may also precede the onset of the disease. In their original article, Hoehn and Yahr listed generalized fatigue as the presenting symptom in 2 % of patients with PD [64]. In patients with more advanced disease, cross-sectional studies found prevalence rates between 40 % and 56 %, and the frequency of fatigue was found to be even higher (75 %) during off-state [172]. In the only population-based longitudinal study to date, fatigue prevalence increased from 35.7 % to 55.7 % during eight years of follow-up [9]. This increase was related to disease progression, depression and excessive daytime sleepiness (EDS). However, in patients without depression and EDS more than 1/3 of subjects still complained about fatigue, indicating that fatigue in PD may occur independently from other non-motor problems with possible overlapping symptomatology. In more than half of patients, fatigue was a persistent feature when once experienced [9]. Fatigue has substantial negative impact on cognitive and physical function, and quality of life in patients with the disease [42, 61].

Sleep disorders

During the last decade, scientific research has resulted in increased understanding of sleep/wake regulation [136]. It is now clear that several brainstem nuclei and their communicating pathways in the ascending arousing system through the hypothalamus and thalamus to the cortex play key roles in sleep disorders [98, 136]. As Lewy bodies and cell loss are found in these areas in PD, it is anticipated that disturbances of sleep and alertness, including *insomnia*, *hypersomnia*, and *parasomnias*, may be experienced by a large number of patients with PD and other α-synucleinopathies, such as MSA [14]. In addition to pathological changes in brain areas crucial for regulation of sleep and wakefulness, other conditions may contribute to sleep disorders in patients with PD, such as depression and drug treatment. Dopaminergic drugs, particularly dopamine agonists, have been linked to different sleep complaints including insomnia, EDS, and sudden sleep attacks [119, 135].

Insomnia is the most common sleeping problem in PD. In a population-based prevalence study, 60 % of patients complained about nocturnal sleeping problems after in average nine years of disease duration [153]. In most of them, sleep fragmentation and early awakening were the major problems. In the same population, these sleeping problems were found to be one of the main contributors to reduced quality of life [78]. A longitudinal study of this cohort revealed similar prevalence rates of insomnia during 8 years of prospective follow-up, but considerable variation in individual patients over time. The presence of insomnia in this longitudinal study was associated with disease duration, depressive symptoms and female gender [50].

EDS is also common in PD [2]. Evidence suggests that daytime somnolence in PD is not a consequence of nocturnal sleeping problems [48, 51]. Clinical EDS has been found in 15 % of PD patients in a population-based cohort with mean disease duration of nine years, compared to only 1 % of EDS in healthy elderly control subjects [51]. Two longitudinal studies of the same population reported an increase of occurrence of EDS to 29 % and 41 % of surviving patients after 4 years and 8 years of follow-up, respectively [48, 51]. EDS was reported as a persistent complaint in the majority of patients and was associated with age, gender, use of dopamine agonists, and disease severity, suggesting multifactorial underlying pathophysiology [48, 51].

REM sleep behavior disorder (RBD) is a parasomnia characterized by prominent motor activity due to loss of the normal skeletal muscle atonia during REM sleep. The clinical main features of RBD are vocalizations and movements of limbs and body, often associated with dreams. They can vary in intensity and duration, potentially leading to injuries of the patients or their bed-partners [26]. Patients with idiopathic RBD have recently been shown to be at increased risk to develop PD and other α-synucleinopathies, and thus RBD may be an early sign of an evolving synucleinopathy [15]. It is particularly common in patients with MSA and DLB [15], and up to one-third of patients with PD are affected [26, 40]. In a population-based prevalence study of PD with 8-year longitudinal follow-up, prevalence of clinically probable RBD varied with time, affecting 14.6–27 % of subjects, and was independently associated with male gender, lower disease severity and higher daily levodopa equivalent doses [49].

The syndromes of *restless legs (RLS)* and *periodic limb movements during sleep (PLMS)* are sleep related features that are associated with each other [25, 108] and common in the elderly in Western populations, in which RLS affects 8 to 10 % of subjects over 65 years of age [6, 134, 159]. Substantially lower prevalence rates of RLS have been found in Asian populations (0.1–1.0 %) [106, 152]. Non-controlled studies of RLS in PD from Europe and Northern and Southern America found RLS to be present in about 20 to 50 % [17, 120]. Controlled studies conducted in Asian populations using currently acknowledged criteria suggest that RLS may be slightly more common in PD. In a case control study from India, 7.9 % of PD patients at five years of disease duration complained about RLS compared to only 0.8 % of control subjects [84]. In a more recent study from Singapore, 3.0 % of patients with PD vs. 0.5 % of controls had RLS [95]. To the best of our knowledge, longitudinal studies of RLS in population-based cohorts with PD have not been conducted. RLS in PD usually develops after motor onset of PD and is suggested to be milder than in subjects with idiopathic RLS [116]. Lower plasma ferritin concentrations were found to correlate with the occurrence of RLS in the largest study conducted to date [120], but not in others surveys [84, 116]. Disturbances in central dopaminergic systems are thought to be involved in the etiology of RLS in PD [43, 151].

Autonomic disturbances

Although autonomic dysfunction, particularly orthostatic hypotension, is generally accepted to be a clinical marker of atypical parkinsonian disorders such as MSA, increasing evidence suggests that it is a frequent characteristic also in patients with PD. A recent study of de novo patients with PD found decreased cardiac radioiodinated metaiodobenzylguanidine (MIBG) uptake, indicating that latent sympathetic nervous dysfunction is already present in patients with early, untreated PD [117]. In the same study, MIBG uptake and blood pressure responses decreased with increased disease severity, suggesting that vasomotor cardiac dysfunction is associated with the severity of the disease. This is in line with clinical observations of an increase in autonomic

disturbances as the disease progresses. Symptomatic hypotension is rare in early PD. In a prospective clinic-based study of 51 de novo patients with PD, only one subject showed clinical symptoms of hypotension [16]. In contrast, in a community-based study of prevalent PD patients, 47 % met criteria of orthostatic hypotension [5]. This figure was lower in a prospective clinic-based survey of patients with six years of disease duration and more advanced disease, in which 15.4 % of subjects complained about symptomatic orthostatic hypotension [83]. Other frequently experienced autonomic symptoms in this cohort were hypersalivation (14 %), sexual dysfunction (18 %), urinary problems (22 %), sweating disorder (24 %) and constipation (59 %). In a more recent clinic-based case-control study of patient-reported autonomic features, patients with PD reported significantly more symptoms for all autonomic domains, with the greatest differences to controls in the gastrointestinal and urinary domain [166]. Greater disease severity, higher doses of dopaminergic medication, and advanced age were associated with more frequent autonomic symptoms in this cohort.

Olfactory dysfunction

Olfactory dysfunction in PD includes impairment of odor detection, differentiation, and identification, and is persistent and not influenced by drug treatment [79]. In the light of Braak's hypothesis of a stagewise progression of pathological changes in PD, indicating presymptomatic lesions in the olfactoric tract, attention has been drawn to patients primarily diagnosed with idiopathic hyposmnia. Recent evidence suggests that these persons are at increased risk of developing PD later during life [55, 127, 133]. Of 40 hyposmic, asymptomatic first-degree relatives of PD patients, 10 % developed clinical PD within two years of prospective follow-up [127]. In addition, baseline 123β-CIT SPECT binding ratios of these patients were strongly reduced, indicating a subclinical degenerative process within the dopaminergic nigrostriatal system. In another study [146], 11 of 30 patients with idiopathic olfactory loss exhibited an increased echogenicity of the substantia nigra in transcranial sonography. In 10 of these 11 patients, dopamine transporter SPECT scans were performed. Median uptake ratios in the basal ganglia were pathological in five patients and two further subjects exhibited borderline findings. After four years, 7 % of the 30 subjects had developed clinical symptoms of PD [55].

Olfactory dysfunction is increasingly recognized as a frequent feature in overt PD [105, 111], but its prevalence in the general PD population is unknown. Most patients showing deficits in olfactory tests are unaware of a smell disorder [28, 111]. In a clinic-based study, 38 % of 37 PD subjects reported subjectively normal olfaction at six years of disease duration [111]. However, based on olfactory testing, all 37 subjects had at least moderate hyposmia and about 50 % had anosmia [111].

Prognosis and socioeconomic consequences of PD

PD is chronic and progressive, and currently incurable. Life expectancy is decreased despite modern treatment. In their classic article, Hoehn and Yahr reported a standardized mortality ratio (SMR) of 2.9 [64]. SMR derived from more recent studies range from 1.3 to 4.1 [62, 101]. Methodological differences are likely to account for this variation. In the Olmstead County study, median survival of patients from diagnosis was 10.3 years [30]. In the Sydney Multicentre Study following de novo patients prospectively over time, median time from motor onset to death was 12.2 years [60]. Disease severity, dementia and, with some inconsistency, age are independent risk factors for increased mortality in PD [62, 101]. The cause of death in patients with PD are often related to immobility, and fatal infections are not unusual [12].

Several studies from Western and Northern European countries suggest that the disease is costly for patients and the society [38, 56, 80, 147]. In a Swedish survey the total annual cost of the disease was estimated to be 13,800 Euros per individual [56]. Due to the progressive nature of PD, costs increase with disease severity. Direct annual costs were estimated to be nearly 30,000 Euros for those in Hoehn and Yahr stage V, and nursing home placement was associated with a cost increase of approximately 500 % in English patients [38]. Due to the aging population, the economic burden of PD is expected to further increase in the future.

Conclusion

PD is the second most common neurodegenerative disorder. PD is chronic and progressive, and mortality is increased despite modern treatment. Due to lack of valid diagnostic biomarkers, the diagnosis of PD during lifetime relies on clinical criteria. Age-standardized incidence rates of PD in population-based studies from Europe and the USA using strict diagnostic criteria range from 8.6 to 19 per 100,000 inhabitants. The disease cause is considered to be multifactorial, with interplay between environmental factors and genetic susceptibility, and aging-related processes. Non-motor features such as constipation, olfactory dysfunction, depression, anxiety, and sleep disorders may precede the motor onset of the disease which is defined by the presence of at least two of the four cardinal motor signs resting tremor, rigidity, bradykinesia, and postural abnormalities. Overall motor severity progresses slowly, with annual progression rates ranging from 1.5–3 % in population-based studies.

After about six years of disease duration, 22–40 % of patients in community-based samples have developed motor fluctuations. In general, the frequency and severity of non-motor features increases during the clinical course of the disease. In advanced stages, the vast majority of patients have experienced non-motor problems such as hypersomnia, apathy, fatigue, psychotic symptoms, cognitive impairment, or dementia. Prevalence figures of these features, however, vary considerably, most probably due to methodological differences between studies. In addition, there is a lack of population-based longitudinal studies on several PD related features, such as motor complications, psychosis, apathy, and autonomic dysfunction.

Future needs in PD epidemiology include (i) a better characterization of the premotor phase with respect to its duration and associated features, (i) validation of accuracy of established diagnostic criteria when applied early during the course of the disease, (iii) development and validation of disease-specific diagnostic criteria for non-motor features, and (iv) prospective long-term studies of representative incident cohorts with careful assessment of motor and non-motor features.

Conflict of interest The authors declare no conflict of interest.

Acknowledgement This article is part of *Journal of Neurology (J Neurol , 2008, 255, Suppl 5).* Publication of this supplement has been funded by an unrestricted grant from GlaxoSmithKline. GlaxoSmithKline has had no editorial control with respect to the articles contained in this publication.

References

1. (1993) Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group. N Engl J Med 328:176–183
2. Adler CH, Thorpy MJ (2005) Sleep issues in Parkinson's disease. Neurology 64:S12–S20
3. Ahlskog JE, Muenter MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 16:448–458
4. Allam MF, Del Castillo AS, Navajas RF (2005) Parkinson's disease risk factors: genetic, environmental, or both? Neurol Res 27:206–208
5. Allcock LM, Ullyart K, Kenny RA, Burn DJ (2004) Frequency of orthostatic hypotension in a community based cohort of patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 75:1470–1471
6. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L (2005) Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 165:1286–1292
7. Alves G, Kurz M, Lie SA, Larsen JP (2004) Cigarette smoking in Parkinson's disease: influence on disease progression. Mov Disord 19:1087–1092
8. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D (2006) Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord 21:1123–1130
9. Alves G, Wentzel-Larsen T, Larsen JP (2004) Is fatigue an independent and persistent symptom in patients with Parkinson disease? Neurology 63: 1908–1911
10. Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP (2005) Progression of motor impairment and disability in Parkinson disease: a population-based study. Neurology 65:1436–1441
11. Autere JM, Moilanen JS, Myllyla VV, Majamaa K (2000) Familial aggregation of Parkinson's disease in a Finnish population. J Neurol Neurosurg Psychiatry 69:107–109
12. Beyer MK, Herlofson K, Arsland D, Larsen JP (2001) Causes of death in a community-based study of Parkinson's disease. Acta Neurol Scand 103:7–11
13. Bhidayasiri R, Truong DD (2008) Motor complications in Parkinson disease: clinical manifestations and management. J Neurol Sci 266:204–215
14. Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE (2001) Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 16:622–630
15. Boeve BF, Silber MH, Parisi JE, Dickson DW, Ferman TJ, Benarroch EE, Schmeichel AM, Smith GE, Petersen RC, Ahlskog JE, Matsumoto JY, Knopman DS, Schenck CH, Mahowald MW (2003) Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 61:40–45
16. Bonuccelli U, Lucetti C, Del Dotto P, Ceravolo R, Gambaccini G, Bernardini S, Rossi G, Piaggesi A (2003) Orthostatic hypotension in de novo Parkinson disease. Arch Neurol 60:1400–1404
17. Braga-Neto P, da Silva-Junior FP, Sueli Monte F, de Bruin PF, de Bruin VM (2004) Snoring and excessive daytime sleepiness in Parkinson's disease. J Neurol Sci 217:41–45
18. Bronnick K, Emre M, Lane R, Tekin S, Aarsland D (2007) Profile of cognitive impairment in dementia associated with Parkinson's disease compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry 78:1064–1068
19. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211

20. Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA (2005) Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 64:1404–1410
21. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG (2006) Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 77:585–589
22. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D (2008) Dementia and survival in Parkinson disease: a 12-year population study. Neurology 70:1017–1022
23. Cairns V, Godwin J (2005) Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 34:1340–1345
24. Chaudhuri A, Behan PO (2004) Fatigue in neurological disorders. Lancet 363: 978–988
25. Coleman RM, Pollak CP, Weitzman ED (1980) Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. Ann Neurol 8:416–421
26. Comella CL, Nardine TM, Diederich NJ, Stebbins GT (1998) Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology 51:526–529
27. de Maindreville AD, Fenelon G, Mahieux F (2005) Hallucinations in Parkinson's disease: a follow-up study. Mov Disord 20:212–217
28. Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI (1992) Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 55:138–142
29. Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244:2–8
30. Elbaz A, Bower JH, Peterson BJ, Maraganore DM, McDonnell SK, Ahlskog JE, Schaid DJ, Rocca WA (2003) Survival study of Parkinson disease in Olmsted County, Minnesota. Arch Neurol 60: 91–96
31. Elbaz A, Tranchant C (2007) Epidemiologic studies of environmental exposures in Parkinson's disease. J Neurol Sci 262:37–44
32. Eriksen JL, Wszolek Z, Petrucelli L (2005) Molecular pathogenesis of Parkinson disease. Arch Neurol 62: 353–357
33. Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 991:1–14
34. Fahn S, Elton RL (1987) Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DM, Lieberman A (eds) Recent development in Parkinson's disease. MacMillan Health Care Information, Florham Park, NJ, pp 153–163
35. Fenelon G (2008) Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and current understanding of pathophysiologic mechanisms. CNS Spectr 13:18–25
36. Fenelon G, Goetz CG, Karenberg A (2006) Hallucinations in Parkinson disease in the prelevodopa era. Neurology 66:93–98
37. Fenelon G, Mahieux F, Huon R, Ziegler M (2000) Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 123(Pt 4): 733–745
38. Findley L, Aujla M, Bain PG, Baker M, Beech C, Bowman C, Holmes J, Kingdom WK, MacMahon DG, Peto V, Playfer JR (2003) Direct economic impact of Parkinson's disease: a research survey in the United Kingdom. Mov Disord 18:1139–1145
39. Foltynie T, Brayne CE, Robbins TW, Barker RA (2004) The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 127:550–560
40. Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J, Montplaisir J (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59:585–589
41. Gandhi S, Wood NW (2005) Molecular pathogenesis of Parkinson's disease. Hum Mol Genet 14:2749–2755
42. Garber CE, Friedman JH (2003) Effects of fatigue on physical activity and function in patients with Parkinson's disease. Neurology 60:1119–1124
43. Garcia-Borreguero D, Larrosa O, Bravo M (2003) Parkinson's disease and sleep. Sleep Med Rev 7:115–129
44. Garcia Ruiz PJ, Meseguer E, Del Val J, Vazquez A, Sanchez Bernardos V, Vazquez A (2004) Motor complications in Parkinson disease: a prospective follow-up study. Clin Neuropharmacol 27:49–52
45. Gasser T, Muller-Myhsok B, Wszolek ZK, Oehlmann R, Calne DB, Bonifati V, Bereznai B, Fabrizio E, Vieregge P, Horstmann RD (1998) A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet 18: 262–265
46. Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. Arch Neurol 56:33–39
47. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, Tanner C (2001) Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 56: 1712–1721
48. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP (2006) Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology 67:853–858
49. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP (2008) Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry 79: 387–391
50. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP (2007) Insomnia in Parkinson's disease: frequency and progression over time. J Neurol Neurosurg Psychiatry 78:476–479
51. Gjerstad MD, Aarsland D, Larsen JP (2002) Development of daytime somnolence over time in Parkinson's disease. Neurology 58:1544–1546
52. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB (2001) Prospective longitudinal assessment of hallucinations in Parkinson's disease. Neurology 57:2078–2082
53. Goetz CG, Tanner CM, Stebbins GT, Buchman AS (1988) Risk factors for progression in Parkinson's disease. Neurology 38:1841–1844
54. Grimbergen YA, Munneke M, Bloem BR (2004) Falls in Parkinson's disease. Curr Opin Neurol 17:405–415
55. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H (2007) Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 22:839–842
56. Hagell P, Nordling S, Reimer J, Grabowski M, Persson U (2002) Resource use and costs in a Swedish cohort of patients with Parkinson's disease. Mov Disord 17:1213–1220
57. Haugarvoll K, Rademakers R, Kachergus JM, Nuytemans K, Ross OA, Gibson JM, Tan EK, Gaig C, Tolosa E, Goldwurm S, Guidi M, Riboldazzi G, Brown L, Walter U, Benecke R, Berg D, Gasser T, Theuns J, Pals P, Cras P, De Deyn PP, Engelborghs S, Pickut B, Uitti RJ, Foroud T, Nichols WC, Hagenah J, Klein C, Samii A, Zabetian CP, Bonifati V, Van Broeckhoven C, Farrer MJ, Wszolek ZK (2008) Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease. Neurology 70:1456–1460
58. Hauser RA, McDermott MP, Messing S (2006) Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. Arch Neurol 63:1756–1760

59. Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Broe GA, Adena MA (1995) Age at onset: the major determinant of outcome in Parkinson's disease. Acta Neurol Scand 92:455–463
60. Hely MA, Morris JG, Reid WG, Trafficante R (2005) Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 20:190–199
61. Herlofson K, Larsen JP (2003) The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 107: 1–6
62. Herlofson K, Lie SA, Arsland D, Larsen JP (2004) Mortality and Parkinson disease: A community based study. Neurology 62:937–942
63. Hilker R, Schweitzer K, Coburger S, Ghaemi M, Weisenbach S, Jacobs AH, Rudolf J, Herholz K, Heiss WD (2005) Nonlinear progression of Parkinson disease as determined by serial positron emission tomographic imaging of striatal fluorodopa F 18 activity. Arch Neurol 62:378–382
64. Hoehn M, Yahr M (1967) Parkinsonism: Onset, progression, and mortality. Neurology 17:427–442
65. Hoehn MM, Yahr MD (1967) Parkinsonism: Onset, progression and mortality. Neurology 17:427–442
66. Holroyd S, Currie L, Wooten GF (2001) Prospective study of hallucinations and delusions in Parkinson's disease. J Neurol Neurosurg Psychiatry 70: 734–738
67. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ (1992) What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinicopathologic study. Neurology 42:1142–1146
68. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ (2002) The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 125:861–870
69. Hughes AJ, Daniel SE, Blankson S, Lees AJ (1993) A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 50:140–148
70. Hughes AJ, Daniel SE, Lees AJ (1993) The clinical features of Parkinson's disease in 100 histologically proven cases. Adv Neurol 60:595–599
71. Hughes AJ, Daniel SE, Lees AJ (2001) Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 57:1497–1499
72. Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, Spokes EG (2000) A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology 54:1596–1602
73. Hui JS, Murdock GA, Chung JS, Lew MF (2005) Behavioral changes as side effects of medication treatment for Parkinson's disease. Adv Neurol 96: 114–129
74. Isella V, Melzi P, Grimaldi M, Iurlaro S, Piolti R, Ferrarese C, Frattola L, Appollonio I (2002) Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. Mov Disord 17:366–371
75. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, et al. (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 40:1529–1534
76. Janvin C, Aarsland D, Larsen JP, Hugdahl K (2003) Neuropsychological profile of patients with Parkinson's disease without dementia. Dement Geriatr Cogn Disord 15:126–131
77. Kandinov B, Giladi N, Korczyn AD (2007) The effect of cigarette smoking, tea, and coffee consumption on the progression of Parkinson's disease. Parkinsonism Relat Disord 13:243–245
78. Karlsen KH, Larsen JP, Tandberg E, Maeland JG (1999) Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 66:431–435
79. Katzenschlager R, Zijlmans J, Evans A, Watt H, Lees AJ (2004) Olfactory function distinguishes vascular parkinsonism from Parkinson's disease. J Neurol Neurosurg Psychiatry 75:1749–1752
80. Keranen T, Kaakkola S, Sotaniemi K, Laulumaa V, Haapaniemi T, Jolma T, Kola H, Ylikoski A, Satomaa O, Kovanen J, Taimela E, Haapaniemi H, Turunen H, Takala A (2003) Economic burden and quality of life impairment increase with severity of PD. Parkinsonism Relat Disord 9:163–168
81. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392: 605–608
82. Koller WC, Hutton JT, Tolosa E, Capilldeo R (1999) Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology 53:1012–1019
83. Korchounov A, Kessler KR, Yakhno NN, Damulin IV, Schipper HI (2005) Determinants of autonomic dysfunction in idiopathic Parkinson's disease. J Neurol 252:1530–1536
84. Krishnan PR, Bhatia M, Behari M (2003) Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord 18:181–185
85. Kurz M, Alves G, Aarsland D, Larsen JP (2003) Familial Parkinson's disease: a community-based study. Eur J Neurol 10:159–163
86. Lai BC, Marion SA, Teschke K, Tsui JK (2002) Occupational and environmental risk factors for Parkinson's disease. Parkinsonism Relat Disord 8:297–309
87. Larsen JP, Karlsen K, Tandberg E (2000) Clinical problems in non-fluctuating patients with Parkinson's disease: a community-based study. Mov Disord 15:826–829
88. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR (2003) Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord 18:414–418
89. Leroy E, Anastasopoulos D, Konitsiotis S, Lavedan C, Polymeropoulos MH (1998) Deletions in the Parkin gene and genetic heterogeneity in a Greek family with early onset Parkinson's disease. Hum Genet 103:424–427
90. Levy G, Schupf N, Tang MX, Cote LJ, Louis ED, Mejia H, Stern Y, Marder K (2002) Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol 51: 722–729
91. Levy G, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, Stern Y, Marder K (2000) Motor impairment in PD: relationship to incident dementia and age. Neurology 55:539–544
92. Levy G, Tang MX, Louis ED, Cote LJ, Alfaro B, Mejia H, Stern Y, Marder K (2002) The association of incident dementia with mortality in PD. Neurology 59:1708–1713
93. Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I (1998) Apathy is not depression. J Neuropsychiatry Clin Neurosci 10:314–319
94. Litvan I (1998) Parkinsonian features: when are they Parkinson disease? Jama 280:1654–1655
95. Loo HV, Tan EK (2008) Case-control study of restless legs syndrome and quality of sleep in Parkinson's disease. J Neurol Sci 266:145–149
96. Lou JS, Kearns G, Oken B, Sexton G, Nutt J (2001) Exacerbated physical fatigue and mental fatigue in Parkinson's disease. Mov Disord 16:190–196
97. Louis ED, Tang MX, Cote L, Alfaro B, Mejia H, Marder K (1999) Progression of parkinsonian signs in Parkinson disease. Arch Neurol 56:334–337
98. Lu J, Jhou TC, Saper CB (2006) Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. J Neurosci 26:193–202

99. Marder K, Tang MX, Cote L, Stern Y, Mayeux R (1995) The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol 52:695–701
100. Marin RS (1991) Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3:243–254
101. Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Rudolph A, Lang AE (2005) Survival in Parkinson disease: thirteen-year follow-up of the DATATOP cohort. Neurology 64:87–93
102. Marras C, Rochon P, Lang AE (2002) Predicting motor decline and disability in Parkinson disease: a systematic review. Arch Neurol 59:1724–1728
103. McKeith IG (2006) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis 9:417–423
104. Meara J, Bhowmick BK, Hobson P (1999) Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing 28:99–102
105. Mesholam RI, Moberg PJ, Mahr RN, Doty RL (1998) Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol 55:84–90
106. Mizuno S, Miyaoka T, Inagaki T, Horiguchi J (2005) Prevalence of restless legs syndrome in non-institutionalized Japanese elderly. Psychiatry Clin Neurosci 59:461–465
107. Mjones H (1949) Paralysis agitans: a clinical and genetic study. Acta Psychiatr Neurol Scand 54(Suppl): 1–195
108. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P (1997) Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 12:61–65
109. Morrish PK (2003) How valid is dopamine transporter imaging as a surrogate marker in research trials in Parkinson's disease? Mov Disord 18(Suppl 7):S63–S70
110. Morrish PK, Sawle GV, Brooks DJ (1996) An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. Brain 119(Pt 2): 585–591
111. Muller A, Reichmann H, Livermore A, Hummel T (2002) Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. J Neural Transm 109:805–811
112. Muller J, Wenning GK, Jellinger K, McKee A, Poewe W, Litvan I (2000) Progression of Hoehn and Yahr stages in Parkinsonian disorders: a clinicopathologic study. Neurology 55: 888–891
113. Myslobodsky M, Lalonde FM, Hicks L (2001) Are patients with Parkinson's disease suicidal? J Geriatr Psychiatry Neurol 14:120–124
114. Nilsson FM, Kessing LV, Bolwig TG (2001) Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. Acta Psychiatr Scand 104: 380–386
115. Nilsson FM, Kessing LV, Sorensen TM, Andersen PK, Bolwig TG (2002) Major depressive disorder in Parkinson's disease: a register-based study. Acta Psychiatr Scand 106:202–211
116. Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K (2006) Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord 21:380–384
117. Oka H, Mochio S, Onouchi K, Morita M, Yoshioka M, Inoue K (2006) Cardiovascular dysautonomia in de novo Parkinson's disease. J Neurol Sci 241:59–65
118. Olanow CW (2007) The pathogenesis of cell death in Parkinson's disease – 2007. Mov Disord 22(Suppl 17): S335–S342
119. Olanow CW, Schapira AH, Roth T (2000) Waking up to sleep episodes in Parkinson's disease. Mov Disord 15: 212–215
120. Ondo WG, Vuong KD, Jankovic J (2002) Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol 59: 421–424
121. Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, Lopez de Munain A, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de Silva R, Lees A, Marti-Masso JF, Perez-Tur J, Wood NW, Singleton AB (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44:595–600
122. Patel V, Kirkwood BR, Weiss H, Pednekar S, Fernandes J, Pereira B, Upadhye M, Mabey D (2005) Chronic fatigue in developing countries: population based survey of women in India. BMJ 330:1190
123. Perry EK, McKeith I, Thompson P, Marshall E, Kerwin J, Jabeen S, Edwardson JA, Ince P, Blessed G, Irving D, et al. (1991) Topography, extent, and clinical relevance of neurochemical deficits in dementia of Lewy body type, Parkinson's disease, and Alzheimer's disease. Ann N Y Acad Sci 640:197–202
124. Pickering RM, Grimbergen YA, Rigney U, Ashburn A, Mazibrada G, Wood B, Gray P, Kerr G, Bloem BR (2007) A meta-analysis of six prospective studies of falling in Parkinson's disease. Mov Disord 22: 1892–1900
125. Pluck GC, Brown RG (2002) Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry 73:636–642
126. Poewe WH, Wenning GK (1998) The natural history of Parkinson's disease. Ann Neurol 44:S1–S9
127. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters E, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 56:173–181
128. Post B, Merkus MP, de Haan RJ, Speelman JD (2007) Prognostic factors for the progression of Parkinson's disease: a systematic review. Mov Disord 22:1839–1851; quiz 1988
129. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ (2002) Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord 17:867–876
130. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, Aarsland D, Babcock D, Cummings J, Endicott J, Factor S, Galpern W, Lees A, Marsh L, Stacy M, Gwinn-Hardy K, Voon V, Goetz C (2007) Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord 22: 1061–1068
131. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF (2008) A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 23:183–189; quiz 313
132. Rippon GA, Marder KS (2005) Dementia in Parkinson's disease. Adv Neurol 96:95–113
133. Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, Launer L, White LR (2008) Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 63:167–173
134. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K (2000) Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 54:1064–1068

135. Rye DB, Bliwise DL, Dihenia B, Gurecki P (2000) FAST TRACK: daytime sleepiness in Parkinson's disease. J Sleep Res 9:63–69
136. Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. Nature 437: 1257–1263
137. Scherfler C, Schwarz J, Antonini A, Grosset D, Valldeoriola F, Marek K, Oertel W, Tolosa E, Lees AJ, Poewe W (2007) Role of DAT-SPECT in the diagnostic work up of parkinsonism. Mov Disord 22:1229–1238
138. Schrag A, Ben-Shlomo Y, Quinn N (2002) How common are complications of Parkinson's disease? J Neurol 249:419–423
139. Schrag A, Ben-Shlomo Y, Quinn N (2002) How valid is the clinical diagnosis of Parkinson's disease in the community? J Neurol Neurosurg Psychiatry 73:529–534
140. Schrag A, Dodel R, Spottke A, Bornschein B, Siebert U, Quinn NP (2007) Rate of clinical progression in Parkinson's disease. A prospective study. Mov Disord 22:938–945
141. Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 69:308–312
142. Seppi K, Schocke MF (2005) An update on conventional and advanced magnetic resonance imaging techniques in the differential diagnosis of neurodegenerative parkinsonism. Curr Opin Neurol 18:370–375
143. Shiba M, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA (2000) Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 15:669–677
144. Shulman LM (2007) Gender differences in Parkinson's disease. Gend Med 4:8–18
145. Shulman LM, Taback RL, Bean J, Weiner WJ (2001) Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord 16:507–510
146. Sommer U, Hummel T, Cormann K, Mueller A, Frasnelli J, Kropp J, Reichmann H (2004) Detection of presymptomatic Parkinson's disease: combining smell tests, transcranial sonography, and SPECT. Mov Disord 19:1196–1202
147. Spottke AE, Reuter M, Machat O, Bornschein B, von Campenhausen S, Berger K, Koehne-Volland R, Rieke J, Simonow A, Brandstaedter D, Siebert U, Oertel WH, Ulm G, Dodel R (2005) Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 23:817–836
148. Stenager EN, Wermuth L, Stenager E, Boldsen J (1994) Suicide in patients with Parkinson's disease. An epidemiological study. Acta Psychiatr Scand 90:70–72
149. Stolze H, Klebe S, Zechlin C, Baecker C, Friege L, Deuschl G (2004) Falls in frequent neurological diseases – prevalence, risk factors and aetiology. J Neurol 251:79–84
150. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ (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 66: 968–975
151. Tan EK (2006) Restless legs syndrome and Parkinson's disease: is there an etiologic link? J Neurol 253(Suppl 7): VII33–VII37
152. Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK (2001) Restless legs syndrome in an Asian population: A study in Singapore. Mov Disord 16:577–579
153. Tandberg E, Larsen JP, Karlsen K (1998) A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 13: 895–899
154. Tandberg E, Larsen JP, Aarsland D, Cummings JL (1996) The occurrence of depression in Parkinson's disease. A community-based study. Arch Neurol 53:175–179
155. Tandberg E, Larsen JP, Aarsland D, Laake K, Cummings JL (1997) Risk factors for depression in Parkinson disease. Arch Neurol 54:625–630
156. Tanner CM, Aston DA (2000) Epidemiology of Parkinson's disease and akinetic syndromes. Curr Opin Neurol 13:427–430
157. Taylor KS, Cook JA, Counsell CE (2007) Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry 78: 905–906
158. Tetrud JW, Langston JW (1989) The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Science 245:519–522
159. Tison F, Crochard A, Leger D, Bouee S, Lainey E, El Hasnaoui A (2005) Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT Study. Neurology 65:239–246
160. Tolosa E, Compta Y, Gaig C (2007) The premotor phase of Parkinson's disease. Parkinsonism Relat Disord 13(Suppl):S2–S7
161. Twelves D, Perkins KS, Counsell C (2003) Systematic review of incidence studies of Parkinson's disease. Mov Disord 18:19–31
162. Uitti RJ, Baba Y, Wszolek ZK, Putzke DJ (2005) Defining the Parkinson's disease phenotype: initial symptoms and baseline characteristics in a clinical cohort. Parkinsonism Relat Disord 11:139–145
163. Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, Albanese A, Wood NW (2001) Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35–p36. Am J Hum Genet 68: 895–900
164. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, Nelson LM (2003) Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 157:1015–1022
165. van Duijn CM, Dekker MC, Bonifati V, Galjaard RJ, Houwing-Duistermaat JJ, Snijders PJ, Testers L, Breedveld GJ, Horstink M, Sandkuijl LA, van Swieten JC, Oostra BA, Heutink P (2001) Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet 69:629–634
166. Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, van Hilten JJ (2007) Patient-reported autonomic symptoms in Parkinson disease. Neurology 69:333–341
167. Verhagen L (2006) Depression in Parkinson's disease: epidemiology and clinical features. In: Woltes EC, Berendse HW, Stam CJ (eds) Mental dysfunction in Parkinson's disease III. VU University Press, Amsterdam, pp 176–188
168. von Campenhausen S, Bornschein B, Wick R, Botzel K, Sampaio C, Poewe W, Oertel W, Siebert U, Berger K, Dodel R (2005) Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 15:473–490
169. White L, Petrovitch H, Ross GW, Masaki KH, Abbott RD, Teng EL, Rodriguez BL, Blanchette PL, Havlik RJ, Wergowske G, Chiu D, Foley DJ, Murdaugh C, Curb JD (1996) Prevalence of dementia in older Japanese-American men in Hawaii: The Honolulu-Asia Aging Study. Jama 276: 955–960
170. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA (2007) Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130:1787–1798
171. Williams DR, Watt HC, Lees AJ (2006) Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. J Neurol Neurosurg Psychiatry 77:468–473

172. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Cherif AA (2002) Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 59:408–413
173. Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 44:601–607
174. Aarsland D, Alves G, Larsen JP (2005) Disorders of motivation, sexual conduct, and sleep in Parkinson's disease. Adv Neurol 96:56–64
175. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003) Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 60:387–392
176. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P (2001) Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 56: 730–736
177. Aarsland D, Andersen K, Larsen JP, Perry R, Wentzel-Larsen T, Lolk A, Kragh-Sorensen P (2004) The rate of cognitive decline in Parkinson disease. Arch Neurol 61:1906–1911
178. Aarsland D, Kvaloy JT, Andersen K, Larsen JP, Tang MX, Lolk A, Kragh-Sorensen P, Marder K (2007) The effect of age of onset of PD on risk of dementia. J Neurol 254:38–45
179. Aarsland D, Larsen JP, Cummins JL, Laake K (1999) Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol 56:595–601
180. Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen K, Tandberg E, Cummings JL (1999) Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 67:492–496
181. Aarsland D, Larsen JP, Tandberg E, Laake K (2000) Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 48:938–942
182. Aasly JO, Toft M, Fernandez-Mata I, Kachergus J, Hulihan M, White LR, Farrer M (2005) Clinical features of LRRK2-associated Parkinson's disease in central Norway. Ann Neurol 57:762–765