An Epidemiological Study of Young and Later Onset Parkinson's Disease

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Dedication

I would like to dedicate this thesis to my late father,

who died unexpectedly and suddenly during my time

in research.

He and my mother provided the love, support,

inspiration and encouragement needed to enable

me to follow my dreams.

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Ethical Statement

Ethical approval was obtained by the Multi-Centre Research Ethical Committee for Wales (05/MRE09/58). All patients with Parkinson's disease and healthy general population controls provided written informed consent to participate in this study.

Thesis Summary

Parkinson's disease (PD) is a common neurodegenerative condition and the risk of developing it is age dependent, the prevalence increasing with advancing age. There are relatively little published data on frequency and clinical features of Young Onset Parkinson's disease (YOPD) and it is uncertain whether this subgroup of PD is a different disease entity to later onset Lewy body PD. Investigation of this question is the main focus of this research thesis.

This work has two components – the first provides an estimate of the prevalence of PD in Cardiff and describes age at onset, the second is a community based case control study of YOPD and later onset PD (LOPD) using the prevalence cohort as the main source of cases.

The prevalence of PD in Cardiff is similar to the weighted average of previous PD prevalence studies in the UK over the past 42 years. Our crude prevalence estimate was 130 per 10^5 (95% CI 117,144) and the age standardised prevalence 142 per 10^5 (95% CI 128,156) using 1997 England and Wales population figures as a standard population.

Significant clinical differences were identified in YOPD as compared to LOPD.

YOPD patients reported less hyposmia, constipation and sleep disturbance in the pre-motor stage, but more depression, paraesthesiae and sleep disturbance and less dementia in established disease than LOPD. YOPD presented more commonly with akinetic rigid symptoms and had a lower frequency of tremor. YOPD was much more likely to involve dystonia and treatment related dyskinesia than LOPD.

These results support the hypothesis that PD is a clinically heterogeneous condition and that significant differences are seen according to age at onset.

Chapter 1 Epidemiological Studies of Parkinson's disease in the UK

1.1 Chapter Summary

Methodological differences can in part explain variation in published incidence and prevalence figures. A recent systematic review of incidence studies of PD has identified areas of improvement when conducting epidemiological studies and makes suggestions as to how future studies should be conducted. We look here at the previously published prevalence studies of PD in the UK and identify similar areas of difficulty when comparing data. We analyse in detail the methodological differences which could explain heterogeneity in previous PD prevalence estimates and suggest how improvements in study design could benefit future studies. This forms the basis of our own prevalence study of PD in Cardiff.

1.2 Introduction

Epidemiological studies are important both for investigating possible aetiologies of disease and for planning health care provision. Data on the incidence and prevalence of Parkinson's disease, the second most common neurodegenerative condition worldwide (de Lau and Breteler 2006), are essential to plan health care services for an ageing population. In addition, temporal and geographic variation may provide clues to possible aetiological factors, and follow up of an incident cohort gives invaluable information on the natural history of the disease.

1.3 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterised by slowness of movement (bradykinesia), increased muscle tone (rigidity), impaired postural reflexes and involuntary shaking (tremor).

1.3.1 Aetiology

The aetiology of PD is unknown. However, recent interest in the genetic aspects of PD has grown due to the discovery of several causative monogenic mutations, although these are likely to explain only a small proportion of all PD (de Lau and Breteler 2006). The exact pathogenic mechanisms underlying selective dopaminergic cell loss in PD are not understood. Possibilities include mitochondrial dysfunction, oxidative stress and protein mishandling (Greenamyre and Hastings 2004). The likely aetiology of non genetic PD, which seemingly accounts for the vast majority of disease, is complex and may involve multiple risk factors. Large, well designed, population based cohort studies are needed to examine the effects of multiple potential risk factors and their interactions as well as effects that develop over time (de Lau and Breteler 2006).

1.3.2 Age at Onset

One risk factor that increases the chance of developing PD is advancing age. Epidemiological studies have reproducibly identified an increasing incidence and prevalence of PD with age, rising after the age of 60 years, although many prevalence studies show a decline in the oldest age groups which is probably artefactual due to under-ascertainment in these groups (Twelves, Perkins *et al.* 2003). Despite this fact, some patients develop the condition at an earlier than expected age. These patients are described as having Young Onset PD (YOPD). Traditionally the exact age definition of YOPD has been variable and arbitrary in the published literature, ranging from less than 40 to less than 55 years. Patients with YOPD must have some exceptional aetiological factor which causes the disease to occur earlier than usual. This may be an unusual environmental exposure or genetic influence, or possibly an interaction of both, or a greater dose of a more common exposure. Studying YOPD in detail and comparing features with "ordinary" late onset PD (LOPD) may provide an insight into the underlying aetiology.

1.3.3 Difficulties in studying PD

The diagnosis of PD can sometimes be difficult and is based on a detailed history and examination. In the early stages of the disease, the diagnosis may be unclear. Diagnostic accuracy is improved with follow up when information on disease course and progression, appearance of additional symptoms and treatment response become

available. There is no definitive diagnostic test in life, and pathological confirmation is required for definite diagnosis after death, a practice which is not common in the UK. The publication of the Queen Square Brain Bank Diagnostic Criteria for PD helped to standardise clinical diagnosis of PD in 1988 (Gibb and Lees 1988). Before the publication of these operational diagnostic criteria the accuracy of physicians' diagnosis during life as compared with pathological confirmation was only 76% in one pivotal study (Hughes, Daniel *et al.* 1992). A more recent study has reported much improved diagnostic accuracy (98.6%) in specialist movement disorder services (Hughes, Daniel *et al.* 2002) However, the diagnostic accuracy may be lower outside specialist clinics. A community based study using GP electronic records revealed that 15% of patients with a diagnosis of PD did not fulfil strict diagnostic criteria, and in approximately 20% of patients with PD, who had already come to medical attention the diagnosis had been missed (Schrag, Ben-Shlomo *et al.* 2002)

The risk of developing PD is much higher with advancing age. However, symptoms of PD may often be confused with "normal" ageing, both by patients and by medical staff, leading to delayed or missed diagnosis. This will obviously affect prevalence estimates, and lead to underestimation of disease burden in the elderly.

Many reports have described clinical differences between young onset and late onset PD. However, most published studies on YOPD are based on small numbers of cases usually from specialist clinics which will be biased towards atypical cases and so may not be representative of YOPD on a population basis. Differences between YOPD and LOPD may be due to differences in pathological processes depending on age at onset, or the effect of age at onset on the same process and other co-morbid conditions which are more common in the elderly. In any case, younger patients with PD are likely to have particular health care and social requirements that need to be acknowledged and addressed.

1.4 Incidence and Prevalence

Incidence of a disease is the rate at which new cases occur in a population during a specified period, usually expressed as an annual incidence. Incidence rates are not affected by differences in survival of patients and so are a direct measure of risk of

disease unlike prevalence estimates (Van Den Eeden, Tanner *et al.* 2003) . However, incidence studies require large cohorts and long follow up periods to generate significant numbers of cases, especially in rare conditions. Also, if follow up of a cohort is incomplete, substantial misclassification may occur, leading to significant underestimation of disease risk (de Lau and Breteler 2006).

Prevalence studies look at the number of existing cases of a disease at a given point in time, given a population at risk. Prevalence estimates are influenced by incidence, survival and migration, but may be more appropriate in studying rarer conditions, as the number of cases will be greater. Also, in diseases where diagnostic accuracy is improved with disease progression, such as Parkinson's disease, there may be less diagnostic uncertainty than in incidence studies.

1.5 Studying Epidemiology of Disease in the UK

The most accurate epidemiological method is a door-to-door survey. However, this is very costly and time consuming as a complete population is screened for disease and potential cases require expert validation. Most UK prevalence studies use the case-finding method looking only at medically diagnosed cases with or without potential missed cases, which is more efficient but will lead to an under-estimation of true prevalence due to the effect of pre-clinical disease.

The UK health care system has particular advantages for medical epidemiology. Health care is available free of cost to all people resident in the UK. Every patient is entitled to register with a primary care general practitioner (GP) who is then responsible for acting as a gate keeper to secondary specialist care in hospitals. It is therefore reasonable to expect that health care in the community is accurately represented in GP records assuming that individuals seek medical advice. By law GPs are required to record clinical problems reported to them by their patients. However, the problem of misdiagnosis remains.

The advent of computerised records in general practice has made identification of prevalent cases of disease more efficient, but inaccuracies still arise when estimating

prevalence relying solely on GP records due to the pitfalls inherent in the electronic coding systems. Therefore more accurate estimates of prevalence use multiple case ascertainment in primary and secondary care.

1.6 Incidence Studies in PD

A systematic review of incidence studies in PD compared previously published data (Twelves, Perkins *et al.* 2003). They found none of the studies used identical methods and this review highlighted significant flaws in the methodologies of these studies including using hospital based case finding strategies, retrospective design and non-standardised inclusion criteria. This may account for some of the variation in reported incidence figures worldwide and makes comparison of studies difficult. Only five studies were directly comparable giving incidence estimates from 8.4 to 19 per 10^5 per year. Most of the studies used both primary care and hospital records but used different methods to identify incident cases. Inclusion criteria varied from defining parkinsonism by the presence of the four cardinal features in older studies to the more strict UK Brian Bank Criteria in more recent ones, as did exclusion criteria and the definition of incident cases. Few studies were prospective (about a quarter) and even fewer (less than ten percent) involved follow up of cases. In just over half the studies were attempts made to confirm the diagnosis by examination of patients by a specialist as part of the study. The systematic review reported the peak incidence of PD was between 70 -79 years of age, although some studies have reported a continued increase in incidence after the age of 80 years. A fifth of the studies reviewed found the incidence of PD was significantly increased in men. In an attempt to overcome problems in the future the authors suggested eight methodological points to which studies should adhere to in an attempt to standardising future epidemiological studies. These are 1) the base population should neither be too small nor too large e.g. between 250,000 to 500,000 is suggested by the authors, 2) the studies should be prospective to maximise case ascertainment and data accuracy, 3) multiple sources should be used to identify possible cases, 4) as many of the potential cases as possible should be seen by an expert in movement disorders, 5) an incident case should be defined by a specific symptom onset rather than date of diagnosis, 6) clear and consistent inclusion and exclusion criteria should be applied, 7) ideally there should be some follow up to give information to support the diagnosis of PD

as per Queen Square Brain Bank Criteria and to assess for symptoms suggestive of a Parkinsonian plus syndrome and 8) incidence rates should be reported by standard age strata to enable comparisons between studies, and confidence intervals should be given. An incidence study was designed in Aberdeen addressing some of the points raised by Twelves and colleagues (Taylor, Counsell *et al.* 2006). This was a large community based incidence study of PD with long term follow up. They utilised multiple sources in primary and secondary care for ascertainment of cases, including a screening questionnaire in all patients over the age of 75 in the participating GP practices. The authors particularly emphasise the importance of long term clinical follow up of the inception cohort in improving the accuracy of incidence figures by improving diagnostic accuracy and to provide unbiased information on prognosis in a representative cohort of patients. Their pilot study found a crude incidence of PD of 22 per 10^5 per year (which is higher than previously published comparable studies), a mean age at diagnosis of 76 years and a higher incidence in men. The authors suggest the higher incidence estimate may be due to better ascertainment of cases in the elderly age group, as previous studies did not screen for disease in this way. This was supported by the older mean age at diagnosis. Eighty percent of this incident cohort had follow up for at least one year, and the diagnosis was changed in 33%, the majority of which occurred in the first year from presentation (Caslake, Moore *et al.* 2008).

Good quality incidence studies, although giving accurate data on disease rates, require large populations and long follow periods to yield reasonable numbers of patients with a degree of diagnostic accuracy. This is a particular problem in studying YOPD. An analysis of incidence trends in PD suggested no variation in incidence rates over a 15 year period (Rocca, Bower *et al.* 2001) however this study was based on the medical record linkage system of Rochester, Minnesota and may have been biased by the differential access to health care which operates in the US.

1.7 Summary of Published PD Prevalence Studies in the UK

We undertook a systemic review of prevalence studies of PD in the UK. Ovid Medline databases spanning the time period 1950 – 2007 was searched using the search terms "Epidemiology" and "Parkinson's Disease" and confined to human and English

language. Abstracts were screened and only original research articles describing prevalence studies of Parkinson's disease carried out in the UK were included. Particular attention was paid to detailed epidemiological methodology, results given as crude and age adjusted rates. To date, there have been seven published studies looking at prevalence of PD in the United Kingdom, spanning the past 42 years, reporting crude PD prevalence ranging from 108-164/100,000.

1.7.1 Carlisle 1966

Brewis *et al* (Brewis, Poskanzer *et al.* 1966) published the first prevalence study of neurological diseases, including PD, in the UK. This study was based on reviewing information gathered from GPs (18 practices), hospital notes from 4 main hospitals, the Ministry of Health medical officer, private consultations from consultant physicians and death certificates. A random sample of the population were subjected to their head of house undergoing interview by standardised questionnaire asking if members of the household had tremor. The diagnosis of the hospital physician was accepted. There are no further details of inclusion or exclusion criteria mentioned in the publication.
Only patients resident in Carlisle were included in the prevalence estimates. The population denominator was taken as the 1961 Census population of Carlisle (71,101). Eighty cases were identified giving a crude prevalence of 112.5 per 10^5, and the age specific prevalence was shown to rise rapidly with advancing age, but fell in patients over 80. The age adjusted rates to the England and Wales population at that time were 114.5 per 10^5.
The authors compared their findings to those of a study performed in Rochester (Kurland) in 1958. Higher rates were found in the Rochester study and continued to rise in the very elderly age groups. The discrepancy in rates is possibly explained by different diagnostic definitions, especially in the elderly age groups, in some studies features of ageing such as slow shuffling gait and stooped posture may have been classed as Parkinsonian syndromes even if they lack tremor or rigidity, which were regarded as important diagnostic features as clinical definitions of PD evolved with time. The authors also note the great variability in GP case note detail suggesting that some diagnostic information may have been missing, therefore highlighting the importance of a composite picture from primary and secondary care.

1.7.2 Northampton 1985

Sutcliffe *et al* (Sutcliffe, Prior *et al.* 1985) used both primary and secondary care records to estimate the prevalence of PD in Northampton. They used the total list size of the participating GP practices as the population denominator and only used secondary care patients who were registered with those practices. Information was gathered by the GPs and physicians using standardised questionnaires. Diagnosis of PD was made based on the essential presence of bradykinesia and rigidity plus or minus rest tremor without cognitive deficit in the first two years of onset. Other forms of parkinsonism were classed as drug induced, post-encephalitic, multi-system atrophy and cerebrovascular.

A pilot study was conducted to establish the validity of GPs filling out these questionnaires by asking a consultant physician to see patients of 4 GPs whilst blinded to the information they had collected on the questionnaires over a period of 4 weeks. The physician had identified more features of PD than the GPs and there was a 66% agreement in identifying tremor, bradykinesia and rigidity between the consultant physician and the 4 GPs.

For the main study, the participating GPs were asked to fill questionnaires for all patients they knew or encountered with PD over a three month period, and the hospital physicians passed names of their known patients to the physician investigator who completed the questionnaires from the case notes and occasionally an assessment if the notes were inadequate.

Seventy two percent of the GPs approached participated, giving a denominator of 208,499 which accounted for 75% of the Northampton district. Only 74 of the 259 parkinsonian patients were examined for validation. Two hundred and twenty six PD patients were identified giving a crude prevalence of 108 per 10^5 (95% CI 95.2, 123.5). The authors report no gender difference but describe an increase in prevalence with advancing age and compared their results to studies performed in Carlisle, Rochester, Finland and Iceland. Again, methodological differences were suggested to account for variation in differences seen, for example, the high prevalence in Iceland is explained by the greater intensity and duration of surveying patients before the prevalence day.

1.7.3 Aberdeen 1986

Mutch *et al* (Mutch, Dingwall-Fordyce *et al.* 1986) used a multisource ascertainment method to estimate the prevalence of PD in Aberdeen. They asked all hospital doctors

and GPs in Aberdeen to refer any known or new cases of PD to them, then used computerised records for inpatients from the Grampian Health Board files, attendance at the department of therapeutics at Aberdeen University, GP medication prescriptions and by examining records from all neurology and medical clinics and visiting all private and local authority homes for the elderly. Information from these sources was used to compile lists which were given to general practices to ask if further cases were known to GPs, district nurses or health visitors. Practice receptionists were given a list of PD medication and asked to notify the team if any patient was prescribed these.

All patients were interviewed and examined by the authors. Information was supplemented by a relative or carer and by medical case notes. In addition, disability was graded using the Hoehn and Yahr scale and a ten point cognitive screen was performed. The diagnosis was based on the presence of two or more of tremor, rigidity, bradykinesia and postural instability. Those with arteriosclerotic, drug induced or post-encephalitic parkinsonism were excluded. If the diagnosis was unclear, the patient was seen by a neurologist.

In total 249 patients were identified as having PD in a population of 151,616 giving a crude prevalence of 164 per 10^5 (no 95% CI given). It was found that about 25% of patients were diagnosed by their GPs, 25% by a neurologist and 15% by a geriatrician. The modal age at onset in men was the 7^{th} decade, in women the 8^{th}. The authors state they used strict diagnostic criteria and examined 98% of cases. Fifteen percent of the referred cases were found not to have PD. Of these, 20% were drug induced parkinsonism. The authors report an increase in prevalence with increasing age, continuing to increase above the 8^{th} decade, with a higher prevalence of PD in the very old, especially in women. This may be explained by the detailed intensive ascertainment methods used in this study (by visiting all elderly care homes). The age at onset median is reported as 60-69 years which had not changed over the previous 25 years. Approximately 35% of cases were felt to have dementia based on the cognitive screen. The authors conclude by stating that PD is increasingly more common in the older population, many of whom are not under any regular review.

1.7.4 Northampton 1995

Sutcliffe *et al* (Sutcliffe and Meara 1995) repeated their study using similar methods to 1985. GPs and hospital consultants were asked to refer any patient known to them with

parkinsonism, on medication used for PD and those with familial tremor. Those referred were seen, questioned and examined in their home, hospital or residential or nursing homes. The diagnosis was based on the Queen Square Brain Bank Diagnostic Criteria for PD.

Three hundred and eighty three PD cases were identified from a population of 302,000, 92.5% of whom were assessed giving a crude prevalence of 121 per 10^5 (no 95% CI given, but when calculated is 114.9-140.3, thus showing no significant change from 1985). Patients were asked to estimate their disease duration and this was used to define cohorts with onset over each of the previous ten years to calculate a yearly incidence. This was estimated as 12 per 10^5 person years.

The authors suggest an increase of PD prevalence over a ten year period but the rates were very similar and presented without confidence intervals (crude 108 vs. 121, and standardised 134 vs. 140). It is noted when the data are reanalysed for age adjusted rates and confidence intervals calculated (see forest plot p71) there is no statistical difference between the rates. The authors comment on an increase in awareness of PD and they were aided by the fact that more GPs had held a disease register. It was suggested that patients were also being diagnosed earlier as the disability profile of cases was different to that of 1985. The authors point out that as the case finding method is dependant on GP and hospital records, prescriptions and referrals, it is likely this prevalence figure is an under estimate as undiagnosed cases are not included. It was noted that prevalence rose sharply after the age of 50 years and that there was a male predominance.

1.7.5 London 2000

Schrag *et al* (Schrag, Ben-Shlomo *et al.* 2000) approached 15 GP practices in London whose total practice size gave a denominator of 121,608. Records were screened for a diagnosis of PD or parkinsonism, antiparkinsonian drugs or a mention of tremor after the age of 50 years. Diagnosis was based on the Queen Square Brain Bank Diagnostic Criteria for PD. Each patient was assessed and if the diagnosis was in doubt a video recording was made and reviewed for secondary confirmation by a movement disorder neurologist. Any case with an isolated classical rest tremor was classed as possible PD and was included in the prevalence estimate. Drug induced and vascular parkinsonism were classified as were Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA), two neurodegenerative Parkinsonian plus syndromes.

Crude prevalence of PD was estimated as 128 per 10^5 (95% CI 109, 150) and adjusted to the 1997 UK population this rose to 168 per 10^5 (95% CI 142, 195).
The authors report that the prevalence of PD in Southern England is similar to that of North England and Scotland, suggesting no marked geographical variation. The prevalence had remained stable over the previous 30 years despite a reduction in mortality for patients under 75 years. The authors report a misdiagnosis of 15% of those labelled with PD and found that 10-20% of cases had come to medical attention but had not been diagnosed, suggesting that the true prevalence may be as high as 200 per 10^5.

1.7.6 Rural North Wales 2005

Hobson *et al* (Hobson and Meara 2004) used primary care prescribing records for antiparkinsonian drugs and interviewed 11 GPs to identify all known cases of PD who were not actively being treated. They also looked at attendance at the local district general hospital, general outpatients and specialist movement disorder clinics as well as the local PD register. They excluded any case with serious mental illness given neuroleptic and anticholinergic medication implying these were drug induced parkinsonism cases. All cases were interviewed and examined.
A total of 112 PD cases were identified giving a crude prevalence of 144 per 10^5 (95% CI 120, 173), and when adjusted to the 1998 UK population this fell to 105 per 10^5 (95% CI 85, 124). No gender heterogeneity was demonstrated.
The authors stated that crude rates were similar to previously reported but the adjusted rate was lower than the London study. There may be a number of possible explanations. One possibility is the selection bias occurring in the London study as the London GPs were linked to neurology specialty clinics therefore leading to higher recruitment rates in the younger population. Other possibilities include that rural mortality is higher in the elderly, or that the frail elderly have limited health care access so there may be a significant proportion of undiagnosed PD in elderly care homes. In addition the prevalence estimates in the North Wales study was diagnosis based rather than symptom onset based as in the London study, so may have lead to an underestimate of true prevalence. The London study also screened patients with isolated tremor which increases the prevalence of previously undiagnosed PD. The authors comment that their estimate is dependant on medically known cases and strict inclusion criteria and so may

have lead to an underestimation of true prevalence. Lastly, the lower rates may also be explained by less effective ascertainment methods or differential rural mortality.

1.7.7 North Tyneside 2006

Porter *et al* (Porter, Macfarlane *et al.* 2006) asked GPs, consultant neurologists, physicians and geriatricians to provide lists of their patients with possible PD. Pharmacy records and case notes from the local PD clinic were also scrutinised. Patients were visited at home and the diagnosis was based on the Queen Square Brain Bank Criteria. If the case notes showed adequate information to fulfil the Brain Bank criteria these cases were also included. Those patients who declined assessment were only included in the prevalence estimate if they had been seen by secondary care. Drug induced and vascular parkinsonism were classified, as well as essential tremor, PSP, MSA and dementia with Lewy bodies (DLB).

Of the 144 potential cases of PD, 14% were found not to fulfil criteria, giving a crude prevalence of 148 per 10^5 (95% CI 124, 174) and when adjusted to the 2001 UK population, 139 per 10^5 (95% CI 116, 162).

It was noted the Aberdeen study had higher prevalence estimates as care homes were visited and screened. The age adjusted rates had not changed over the previous 30 years. The prevalence of cases increases sharply with age, peaking in the over 90 age group. Men had a higher prevalence in the 75-79 age group, females in the over 90 age group. GP records alone gave an incomplete ascertainment picture and there was some level of misdiagnosis, again highlighting the need for a multisource approach.

1.7.8 Discussion of methodological differences in UK published prevalence studies

A review of UK prevalence studies revealed similar problems and inconsistencies to those identified in the systematic review of incidence studies (Twelves, Perkins *et al.* 2003). The earlier studies were based on case referral from physicians and GPs as electronic database systems were not in place. This relies on the physician and GPs' own knowledge of their patients and does not actively search out known cases. These studies also relied on the diagnostic accuracy of the diagnosing physician without scrutiny. Clearly studies including active ascertainment in primary care are likely to be more accurate.

In the early studies there is lack of standardisation of diagnosis. The Queen Square Brain Bank Criteria for the diagnosis of PD were first mentioned in 1992 as diagnostic inclusion criteria for prevalence estimates. Before this inclusion seems to be less standardised and may well have included some non PD cases. Certainly the Parkinsonian plus syndromes such as MSA, PSP and DLB now have published operational diagnostic criteria whereas during the earlier prevalence studies these entities may not have been widely recognised or diagnosed accurately, being misdiagnosed as PD.

Using computerised hospital records was first mentioned in the 1986 study, but systematic searching for diagnostic codes was not used until 2000. The later studies have used electronic search strategies to screen practice databases for potential cases and then used stringent methods to verify diagnosis by examining as many cases as possible or, if failing that, reviewing the case notes in detail.

Some, but not all studies report 95% confidence intervals for their prevalence estimates, others have calculated age adjusted prevalence estimates, but there is no consistency across the studies as to which standard population has been used and how these figures have been reported.

This variation in methodology of case ascertainment and inclusion criteria is probably responsible for some of the regional and temporal differences in reported PD prevalence. No meta-analysis of the published studies has been reported before. This would be useful to determine if there is true heterogeneity within the studies published to date.

No study has been performed estimating the prevalence of PD in urban South Wales. None of the previous studies has reported age at onset and so there are no data in which to base an estimate of the prevalence of Young Onset PD.

1.8 Incidence vs Prevalence in Studying YOPD

In conditions such as PD where diagnostic accuracy improves with disease duration, prevalent cases can be examined with the advantage of time, thus increasing diagnostic

accuracy. When studying rare conditions, such as YOPD, community based prevalence studies can establish a reasonably sized cohort of diagnosed cases in a short period of time as compared with incidence studies where longer ascertainment periods are required to establish adequate numbers of incident cases and an adequate follow up period must have elapsed to ensure a reasonable degree of diagnostic certainty. However, it should be noted that prevalence studies may be biased as patients with more rapidly progressive disease will be under-reported, known as "length bias" in screening studies.

We selected a prevalence study as the best way to investigate YOPD and attempted to follow best practice based on the recommendations of the Twelves analysis and our own review of previous UK prevalence studies.

Chapter 2 Clinical Aspects of Young Onset Parkinson's Disease

2.1 Chapter Summary

Many clinicians view Young Onset Parkinson's Disease (YOPD) as a different condition to Late Onset Parkinson's disease and this has been reinforced by the identification of Mendelian genes that account for some cases of YOPD. A systematic review of OVID Medline for articles relevant to the clinical features of YOPD published in English between 1950 and 2007 was performed. There are very few prospective community based studies which focus on the features of YOPD and a variety of case definitions are used in the literature. Most studies of YOPD are based on specialist clinic referral series. The available evidence suggests that patients with YOPD have: i.) a slower disease progression, ii) an increased rate of dystonia at onset and during treatment, iii) a lower rate of dementia, and iv) an increased rate of dyskinesias in response to L-DOPA treatment. The majority of the available studies do not report patient genotype data, but it is likely that the clinical heterogeneity of PD will be further refined with detailed clinico-genetic studies.

2.2 Introduction

Parkinson's disease (PD) is defined by the clinical features of pathologically diagnosed Lewy body disease with loss of nigro-striatal neurones and the presence of alpha-synuclein containing Lewy bodies(Litvan, Bhatia *et al.* 2003). The disease is progressive, the aetiology is unclear and there are no disease modifying treatments. The risk of developing PD is age dependant, and the incidence increases rapidly over the age of 60 affecting 1-2% of the population over 65 years of age (de Rijk MC 1997; Van Den Eeden, Tanner *et al.* 2003). The relationship between PD and age suggests that cumulative exposure to an environmental factor, and/or an age dependant biological factor, determines its development. The incidence rate of PD at an earlier than usual age (termed Young Onset Parkinson's disease (YOPD)) is small; data from the Kaiser Permanente scheme in Northern California suggested that this was around 1.5 per 100,000 person years for subjects aged less than 50 (Van Den Eeden, Tanner *et al.* 2003). However, previous incidence studies estimate that five to ten percent of all patients with

PD develop symptoms before the age of 50 and 4-7% before the age of 40 (Teravainen, Forgach *et al.* 1986; Koller and Lang 1987; Gershanik 1988; Tanner and Langston 1990; Van Den Eeden, Tanner *et al.* 2003). The identification of Mendelian genes which can cause typical parkinsonism with young onset (three autosomal recessive genes namely *parkin, DJ-1* and *PINK-1*, and two autosomal dominant genes *α- synuclein* and *LRRK2* which may also present in earlier life but are very much rarer), and reports of pathological heterogeneity raise the possibility that YOPD may be different to late onset PD (LOPD) (Morris 2005; Hardy, Cai *et al.* 2006; Klein, Lohmann-Hedrich *et al.* 2007). If this is the case then the advice and treatment given to patients, in particular future disease modifying therapies may need to be tailored according to the age of onset and related parkinsonism/PD sub-type. It is important not to overestimate the clinical relevance of these genetic forms of parkinsonism however appreciating the gene frequencies in the whole population of PD patients. Currently we understand that mutations in the *parkin, PINK1* and *LRRK2* genes together account for at least 3% of all patients with parkinsonism, *parkin* mutations accounting for 10-20% of young onset cases, *PINK1* between 1-8% and *LRRK2* having a usual onset between 50-70 years. In addition, there is ethnic variation in gene frequency in some of these genetic forms of PD such as the commonest *LRRK2* mutation accounting for 40% of PD in those patients with Arab descent and 20% in Ashkenazi Jews. (Klein, Lohmann-Hedrich *et al.* 2007). However in a large incidence study looking at variation by age, gender and ethnicity of newly diagnosed PD patients in Northern California, the incidence of YOPD did not significantly vary by ethnic group but the rates for men were higher than for women (Van Den Eeden, Tanner *et al.* 2003) .

Several clinical differences have been described which distinguish YOPD from LOPD. If these differences are robust then there are several possible explanations: i) varying manifestations of the same disease at different stages of neurological development, ii) disease heterogeneity with variation in cellular and regional pathology or iii) an age dependant effect of co-morbidity. Here, we look at the evidence for separation of PD and parkinsonism based on age at onset and the problems in comparing and interpreting the available data.

2.3 Search Strategy

This review is based on a literature search of the Ovid Medline databases spanning the time period 1950 – 2007 using the following search terms: "Parkison's Disease", "parkinsonian syndrome", "parkinsonism", "paralysis agitans", and "akinetic- rigid syndrome". These were individually combined with each of these search terms: "young onset", "early onset", "age at onset", "juvenile onset". Articles were limited to the English language. Abstracts were screened and articles containing original data from case series and case control studies as well as review articles were included. We have also used the authors' personal knowledge and hand searching of references. A very small number of original research articles describing clinical features of YOPD were found and so any available literature about YOPD was surveyed even where the primary focus of the study was not a comparison of YOPD and LOPD or a clinical case series of YOPD.

2.4 Definition

One of the principal difficulties in studies of YOPD is the terminology and case definition. Various terms have been used to describe PD developing in younger people. Historically, the term juvenile onset has been used to describe what is now termed young or early onset PD and there is considerable overlap in the age definition of these groups amongst different studies (Yokochi M 1981; Yokochi, Narabayashi *et al.* 1984; Gershanik and Leist 1987; Gershanik and Nygaard 1990; Giovannini, Piccolo *et al.* 1991; Yokochi 1997). In 1987 Quinn and colleagues suggested that "juvenile onset parkinsonism" should be reserved for cases with onset before the age of 21 years, and "young onset" for patients with onset between 21 and 40 years (Quinn, Critchley *et al.* 1987; Jankovic 1993). This division was supported by differences in familial aggregation in the two groups. More recent papers, including those reviewing genetic factors, have used the term early onset to describe PD occurring before the age of 45. There is still variation in the upper age limit which defines YOPD, leading to difficulty in comparison between studies. A further issue is whether young onset patients should be described as having parkinsonism, Parkinson's syndrome or Parkinson's disease. In this review we use the term Young Onset PD (YOPD) to describe all patients with younger onset parkinsonism or define the age at onset. The disease entity of PD has been defined by the

presence of Lewy bodies, but only a minority of patients have post-mortem analysis. It is worth emphasizing that many different pathological processes can cause a disease which meets the Queen Square Brain Bank clinical diagnostic criteria for PD (Jellinger 1987; Ward C 1990; Hughes, Daniel *et al.* 1992; Hughes, Daniel *et al.* 2001; Hughes, Daniel *et al.* 2002). Most pathological reports of PD with onset below the age of 21 do not report Lewy body pathology, and recently this has been related to the presence of mutations in *parkin* (Paviour, Surtees *et al.* 2004). Only 3 PD cases with onset before age 21 years have been described with Lewy body pathology at autopsy (Gershanik and Nygaard 1990). However, a brain bank series of 12 YOPD patients (onset before 40 years) and 24 LOPD patients (onset after 70 years) showed no difference in the occurrence of Lewy body pathology although the younger onset cases had greater nigral cell loss and longer disease duration (Gibb and Lees 1988). It seems clear that some, but not all patients with YOPD have Lewy body disease. Very few cases of parkin disease with early onset parkinsonism have come to autopsy, and only two of six have shown evidence of Lewy Bodies (Mori, Kondo *et al.* 1998; Hayashi, Wakabayashi *et al.* 2000; Farrer, Chan *et al.* 2001; van de Warrenburg, Lammens *et al.* 2001; Sasaki, Shirata *et al.* 2004; Pramstaller, Schlossmacher *et al.* 2005) . The limited pathological data suggest that Lewy body pathology is extremely rare with disease onset below the age of 21, but becomes increasingly common with advancing age at onset. This could relate to differences in the underlying diseases or to a greater likelihood of developing Lewy bodies as a pathological response to neurodegeneration with increasing age.

2.5 Disease Progression

A number of studies indicate that YOPD progresses more slowly than LOPD. Variations in measures of disease progression make direct comparison between these studies difficult (Tables 2-1 and 2-2). The majority of studies are retrospective, estimating the rate of progression using a measure of disability at case ascertainment and estimated age at onset to calculate disease duration (Marttila and Rinne 1977; Birkmayer, Riederer *et al.* 1979; Goetz, Tanner *et al.* 1988; Jankovic, McDermott *et al.* 1990; Lee, Schulzer *et al.* 1994; Hely, Morris *et al.* 1995). There are few prospective studies (Diamond, Markham *et al.* 1989; Hely, Morris *et al.* 1995) using change in disability scores during assessments over regular time intervals. Two main methods of relating age at onset to

progression are described. The first compares progression in two groups of patients defined by age at onset (Jankovic, McDermott *et al.* 1990; Lee, Schulzer *et al.* 1994; Hely, Morris *et al.* 1995); the other compares mean age at onset in groups defined by rate of progression (Marttila and Rinne 1977; Birkmayer, Riederer *et al.* 1979; Goetz, Tanner *et al.* 1988; Jankovic, McDermott *et al.* 1990; Hely, Morris *et al.* 1995). By assessing progression both retrospectively and prospectively using both of these methods, the Sydney Multi-Centre Study group concluded that age at symptom onset was the best predictor of marked deterioration in PD symptoms and signs over 5 years (younger onset, slower progression) and this was followed by a second prospective confirmatory study (Diamond, Markham *et al.* 1989; Hely, Morris *et al.* 1995). In the DATATOP (deprenlyl and tocopherol antioxidative therapy of parkinsonism) study of 800 *de novo* PD patients, a retrospective estimate of progression suggested more rapid progression in LOPD (onset at or above age 70) than YOPD (onset at or before age 40) (Jankovic, McDermott *et al.* 1990).

Table 2-1 : Disease Progression YOPD vs LOPD

Study Author	*YOPD/ LOPD (n)*	*AAO YOPD (yrs)*	*Disability measures*	*Study details*		*Conclusion*
Hely (Hely, Morris *et al.* 1995)	90 / 33	< 70	H+Y, Modified Columbia Modified NWUDS	Sydney Multi-Centre Trial	Prospective	YOPD progresses more slowly
Diamond (Diamond, Markham *et al.* 1989)	13 / 26	<50	UCLA score		Prospective	YOPD progresses more slowly
Jankovic (Jankovic, McDermott *et al.* 1990)	33 / 85	≤40	H+Y	DATATOP cohort	Retrospective	Benign group has earlier mean age at onset

Abbreviations: AAO = age at onset, YOPD = young onset Parkinson's disease, LOPD = later onset Parkinson's disease, H+Y = Hoehn and Yahr Scale, NWUDS =Northwest university disability score, DATATOP = deprenyl and tocopherol antioxidative therapy of parkinsonism

Comparing "benign" and "malignant" subsets of 118 untreated PD patients entering the same study, the benign group had a younger mean age at onset. Three further studies have confirmed that YOPD has a slower disease progression (Tables 2-1 and 2-2) (Birkmayer, Riederer *et al.* 1979; Goetz, Tanner *et al.* 1988; Lee, Schulzer *et al.* 1994).

Table 2-2 : Disease progression – Other analysis methods

Study Author	*n*	*Methods*	*Disability measures*	*Patient group*	*Study details*	*Conclusion*
Birkmayer (Birkmayer, Riederer *et al.* 1979)	69	Rapid vs. Slow	Disability score 1-10 in 10 parameters		Retrospective	Younger age at onset correlates with slower progression
Lee (Lee, Schulzer *et al.* 1994)	238	Age at onset categories	UPDRS bradykinesia, practically defined off	Clinic	Retrospective	Younger age at onset correlates with slower progression
Goetz (Goetz, Tanner *et al.* 1988)	62	Rapid vs. Slow	H+Y	Historical cohort		Younger age at onset correlates with slower progression
Martilla (Marttila and Rinne 1977)	442	Rapid vs. Slow	H+Y	Community based		Rapid progressors were older at onset

Abbreviations: UPDRS = Unified Parkinson's disease Rating scale, H+Y = Hoehn and Yahr scale

However, conflicting views have been reported. This may be due to differences in defining disease progression. In a study of 60 YOPD (onset range between 24-39) and 60 LOPD (onset range between 42-68) patients estimating disease progression as the interval from first symptom onset to the development of a bilateral clinical picture (Hoehn and Yahr stage over 2), 60% of the YOPD group developed bilateral involvement within 12 months of onset (termed rapid progressors) compared to 5% of the LOPD group (Giovannini, Piccolo *et al.* 1991). This may reflect earlier bilateral involvement in young onset disease but the relatively short follow-up period in this study means that it is difficult to generalise this finding. Some reports of patients with *parkin* mutations suggest that there is more symmetry in the disruption of striatal dopamine uptake, and neuropathology, than patients with typical LOPD (Portman, Giladi *et al.* 2001; Antonini, Moresco *et al.* 2002; Scherfler, Khan *et al.* 2004). The majority of studies of YOPD are

based on specialist clinic case ascertainment, therefore a further confounding factor is case referral bias. Elderly patients with indolent disease may be more likely to be treated by their non-specialist family practitioners, rather than being referred to specialist clinics, although clearly this will vary in different health care systems. This can only be addressed with community based studies looking at the prevalence of PD classified by age at onset. One study from the 1970's suggests there is no significant correlation between age at onset and disease progression, although there was a trend for older onset patients to progress more rapidly (Marttila and Rinne 1977). Of interest is the higher prevalence of vascular risk factors in LOPD patients, suggesting that the rate of progression in PD patients may be differentially influenced by disease co-morbidity. Concurrent degenerative joint disease or cerebrovascular disease in the older patient may cause an "apparent" more rapid progression to major impairment of gait and balance. Comparing the available evidence is difficult because of the variability in study design and this emphasizes the need for standardised population based studies. The difficulty of measuring progression in PD clinically also applies to studies of disease modifying agents, and a standard methodology would help in defining both phenotypic heterogeneity and the effects of neuroprotection. The majority of the evidence from retrospective clinic based series supports a slower disease progression in YOPD as compared to LOPD.

Whilst this may be a source of some reassurance for younger onset patients, the relative effect of PD on mortality and absolute effect on life expectancy is, if anything, more marked for young onset cases. A previous population-based cohort study of patients with parkinsonism noted that the standardised mortality ratio (SMR) for cases aged 40-50 years at onset was 3.9 (almost four times that of the general population compared to 2.0 for cases aged between 75 to 84 years (Ben-Shlomo and Marmot 1995). The interpretation of this figure requires some caution however as it may consist of patients with multiple system atrophy and progressive supranuclear palsy that have a worse prognosis (Nath, Thomson *et al.* 2005). A recent literature review (Ishihara, Cheesbrough *et al.* 2007) estimated that the life expectancy of patients with onset between 25 to 39 years was 38 years compared to 49 years in the general population resulting in a loss of 11 years life expectancy. The equivalent figures for cases with onset

older than 64 was 5 years compared to 9 years in the general population and hence only a four year loss of life expectancy.

Imaging studies suggest there is lower dopaminergic binding densities in patients with YOPD than LOPD when matched for disease duration, implying that there is greater dopaminergic neuronal loss in YOPD at the point of assessment (Antonini, Moresco *et al.* 2002; Shih, Franco de Andrade *et al.* 2007). Although the majority of these imaging studies are based on patients with *parkin* mutations, one study systematically compared *parkin* positive and *parkin* negative patients and concluded that the pattern of dopaminergic depletion was not dependant on the presence or absence of the mutation (Thobois, Ribeiro *et al.* 2003).

2.6 Parkinsonian Symptoms at Presentation and Dominant Motor Phenotype

Distinctions are made between motor symptoms at presentation and symptom dominance with advancing disease. PD can be classified on the basis of dominant motor phenotype- either tremor-dominant or postural instability with gait disorder (PIGD) dominant (Jankovic, McDermott *et al.* 1990). A proportion of patients with tremor dominant disease at presentation will become predominantly bradykinetic as the disease course advances (Hershey, Feldman *et al.* 1991; Paulus and Jellinger 1991). The importance of recognizing phenotypic patterns in YOPD relates to early diagnosis and prognosis. Several studies have associated motor phenotype with rate of progression. Tremor dominance both at presentation and after 2-7 years from onset are reported to be associated with slower progression (Schwab, England *et al.* 1959; Hoehn and Yahr 1967; Zetusky, Jankovic *et al.* 1985; Huber, Paulson *et al.* 1988; Jankovic, McDermott *et al.* 1990; Hershey, Feldman *et al.* 1991; Biggins, Boyd *et al.* 1992) . There is some suggestion that benign tremulous parkinsonism may in fact be a separate clinical entity with prominent tremor not responding well to L-dopa, minimal progression of other aspects of parkinsonism and often a family history of tremor or PD (Josephs, Matsumoto *et al.* 2006). There is no consensus on tremor frequency in YOPD having been reported less, more and equally as frequently as LOPD (Table 2-3) (Zetusky, Jankovic *et al.* 1985; Gibb and Lees 1988; Giovannini, Piccolo *et al.* 1991; Kostic, Przedborski *et al.* 1991;

Pantelatos and Fornadi 1993; Friedman 1994; Hely, Morris *et al.* 1995; Gomez Arevalo, Jorge *et al.* 1997).

Table 2-3 : Tremor at onset

Study Author	*YOPD/ LOPD*	*AAO YOPD*	*Source of patients*	*Tremor at onset YOPD vs LOPD*	*Difference (%), (95% CI) p-value*	*Conclusions*
Gibb (Gibb and Lees 1988)	46 / 52	<45	Clinic	41% vs. 63%	-22, (-41, -3) p=0.03	Tremor at onset commoner in LOPD
Hely (Hely, Morris *et al.* 1995)	90 / 33	<70	Sydney RCT	42% vs. 64%	-22, (-41, -3) p=0.03	Tremor at onset commoner in LOPD
Freidman (Friedman 1994)	44 / 46	<47	Clinic	34% vs. 59%	-25 (-45, -5) p=0.02	Tremor at onset commoner in LOPD
Kostic (Kostic, Przedborski *et al.* 1991)	25 / 25	< 40	Clinic	32% vs. 36%	-4, (-30, 22) p=0.76	Marginal difference
Quinn (Quinn, Critchley *et al.* 1987)	56 / -	<40	Clinic	52%		52% of YOPD had tremor at onset
Gomez (Gomez Arevalo, Jorge *et al.* 1997)	34 / 34	<40	Clinic	44% vs. 46.4%	-2 (-26, 21) p=0.84	Marginal difference
Giovannini (Giovannini, Piccolo *et al.* 1991)	60 / 60	<40	Clinic	35% vs. 21.7%	13 (-3, 29) p=0.11	Tremor at onset commoner in YOPD but could be chance
Pantelatos (Pantelatos and Fornadi 1993)	221 / 1511	<40	Hospital	No difference (no figures given)		No difference

Abbreviations: AAO = age at onset, YOPD = young onset Parkinson's disease, LOPD = later onset Parkinson's disease, RCT = randomised control trial

It has also been reported that YOPD patients are less likely to have gait difficulty as an early symptom than LOPD (Table 2-4) (Gibb and Lees 1988; Kostic, Przedborski *et al.* 1991; Gomez Arevalo, Jorge *et al.* 1997).

Table 2-4 : Gait Disturbance at Onset

Study Author	*YOPD/ LOPD*	*AAO YOPD*	*Source of patients*	*Gait difficulty at onset YOPD vs LOPD*	*Difference (%), (95% CI) p-value*	*Conclusions*
Gibb (Gibb and Lees 1988)	46 / 52	<45	Clinic	4% vs. 63%	- 59 (-73, -45) p<0.0001	Gait difficulty at onset less common in YOPD
Gomez (Gomez Arevalo, Jorge *et al.* 1997)	34 / 34	<40	Clinic	2.7% vs. 38.8%	-36 (-53, -19) P=0.0002	Gait difficulty at onset less common in YOPD
Kostic(Kostic, Przedborski *et al.* 1991)	25 / 25	< 40	Clinic	4% vs. 16%	-12 (-28, 4) p=0.16	Gait difficulty at onset less common in YOPD

Abbreviations: YOPD = young onset Parkinson's disease, LOPD = later onset Parkinson's disease, AAO = age at onset, CI= confidence interval

This may reflect the confounding effects of age and co-morbidity. Observations may also be biased due to the differential referral of patients to secondary care and misdiagnosis and the presence of tremor is likely to have a significant effect on referral and diagnosis by non-specialists. A community based study in the UK showed that 16% of patients with onset of tremor after the age of 55 years who were diagnosed in the community with non-parkinsonian tremor (usually essential tremor) actually fulfilled the criteria for probable PD on specialist review (Schrag, Ben-Shlomo *et al.* 2002). Younger onset patients are more likely to be referred to specialists, so tremulous PD may be underrepresented in the later onset group ascertained from secondary care. A standardised population based study would attempt to eliminate referral or selection bias capturing data on all patients with PD, not just those referred to secondary care. The available evidence suggests that patients with YOPD have less gait difficulty early in the

disease course than LOPD patients but there is no clear conclusion regarding tremor dominance in YOPD.

2.7 Dystonia

Dystonia, characterized by sustained contraction of muscles leading to abnormal posturing, can occur either pre-treatment, or on treatment as peak-dose or off-period symptoms (Kidron and Melamed 1987). It has been proposed that rest or exercise-induced dystonia at onset (i.e. prior to starting L-dopa treatment) is a common feature of YOPD and was reported to be frequent in Japanese autosomal recessive juvenile parkinsonism (AR-JP) subsequently found to have *parkin* mutations (Yamamura, Sobue *et al.* 1973; Yamamura 1998; Bozi and Bhatia 2003; Khan, Graham *et al.* 2003). PD usually presents with symptoms related to bradykinesia, rigidity or tremor such as difficulty with handwriting or shoulder stiffness.

Dystonia at onset is presumably an alternative manifestation of dopamine deficiency relating to either disease differences or to age related biological differences in the extra-pyramidal system. Dystonia at onset occurs with a frequency of between 14 and 57% in YOPD (Table 2-5). Painful off period dystonia, particularly affecting the feet and ankles also appears to be more common in patients with YOPD occurring at a rate of 30-59% during treatment (Quinn, Critchley *et al.* 1987; Gibb and Lees 1988).

Clinical referral series, without systematic evaluation protocols are the only sources of evidence on dystonia in relation to YOPD. Older patients may be more likely to ascribe dystonia to "muscle cramps" than younger patients and may suggest under recognition or under reporting in LOPD. Overall, the available evidence suggests that both dystonia at onset and treatment related dystonia are more common in young onset PD.

Table 2-5 : Dystonia

Study	*YOPD/ LOPD*	*AAO YOPD*	*Source*	*Dystonia at onset YOPD vs LOPD (95% CI for difference)*	*Treatment Dystonia YOPD vs LOPD*	*Conclusions*
Gomez (Gomez Arevalo, Jorge *et al.* 1997)	34 / 34	<40	Clinic	30.5% vs. 0% (95% CI 15, 46) p=0.0005		Dystonia at onset commoner in YOPD
Tanner (Tanner CM 1985)	21 / 21	<55	Clinic	57% vs. 10% (95% CI 22, 72) p=0.001		Dystonia at onset commoner in YOPD
Gibb (Gibb and Lees 1988)	46 / 52	<45	Clinic	4.3% vs. 0% (95% CI -2, 10) p=0.13	33% vs. 0% (95% CI 19, 47) p<0.0001	
Quinn (Quinn, Critchley *et al.* 1987)	56 / -	<40	Clinic	14%	59%	Treatment related dystonia in nearly 2/3 of YOPD
Gershanik (Gershanik and Leist 1987)	18 / -	<40	Clinic	53%		Dystonia at onset in over half of YOPD
Gershanik (Gershanik and Nygaard 1990)	30 / -		Clinic		50%	Treatment related dystonia in over half of YOPD
Kidron (Kidron and Melamed 1987)	207		Clinic	Early morning dystonia AAO = 53.4 yrs. Off period dystonia AAO = 50 yrs. No dystonia AAO = 60.9 yrs.		

Abbreviations: YOPD = young onset Parkinson's disease, LOPD = later onset Parkinson's disease, AAO = age at onset, CI= confidence interval

2.8 Sleep Benefit

Similarly to dystonia, sleep benefit (a period of lessened disability or feeling "on" upon waking from sleep(Currie, Bennett *et al.* 1997)) may relate to biological differences in the extra-pyramidal systems of younger patients. A number of authors comment that sleep benefit is more common in YOPD, but again these observations are based on highly

selected clinic populations and may not be representative of the true PD population (Yamamura, Sobue *et al.* 1973; Quinn, Critchley *et al.* 1987; Currie, Bennett *et al.* 1997; Yamamura 1998; Bateman, Levett *et al.* 1999).

2.9 Dementia and Neuropsychiatric Features

Cognitive impairment and neuro-psychiatric side effects from medication have been reported to occur less frequently in YOPD. A large body of evidence suggests LOPD patients are at a higher risk of dementia (Granerus 1979; Pederzoli, Girotti *et al.* 1983; Zetusky, Jankovic *et al.* 1985; Hietanen and Teravainen 1988; Ebmeier, Calder *et al.* 1990; Jankovic, McDermott *et al.* 1990; Biggins, Boyd *et al.* 1992), and that the incidence of dementia in YOPD aged under 65 years is negligible (Lieberman, Dziatolowski *et al.* 1979; Elizan, Sroka *et al.* 1986; Portin and Rinne 1987; Quinn, Critchley *et al.* 1987; Hietanen and Teravainen 1988; Reid, Broe *et al.* 1989; Dubois, Pillon *et al.* 1990; Jankovic, McDermott *et al.* 1990; Mayeux, Denaro *et al.* 1992; Stern, Marder *et al.* 1993; Hely, Morris *et al.* 1995). There may be, however, evidence of subtle cognitive involvement in YOPD as compared with the normal population (Hietanen and Teravainen 1988; Dubois, Pillon *et al.* 1990).

In an incident cohort of PD patients defined by the Queen Square Brain Bank criteria observations suggest that older age at PD onset is a risk factor for developing cognitive impairment, although in this study only one patient had disease onset before 40 years (Foltynie, Brayne *et al.* 2004). In a population based study of PD the percentage of patients with dementia increased with age but the prevalent PD cases with and without dementia did not differ with disease duration suggesting that age at onset of PD influences the prevalence of dementia in these patients (Mayeux, Denaro *et al.* 1992). This was challenged by Gibb *et al* (Gibb and Lees 1988) who report the prevalence of not only depression and dementia being similar in YOPD and LOPD but also personality characteristics, such as introversion-extroversion and obsessional qualities. Although some rare genetic subtypes of parkinsonism may involve dementia as a prominent feature such as alpha synuclein triplication or ATP13A2 related atypical parkinsonism (Kufor-Rakeb syndrome, PARK 9) (Muenter, Forno *et al.* 1998; Farrer, Kachergus *et al.* 2004;

Ramirez, Heimbach *et al.* 2006), the overwhelming evidence suggests that YOPD patients suffer less dementia and neuropsychiatric features than LOPD patients, but whether this is a function of ageing rather than age at symptom onset is not fully understood.

2.10 Treatment Response and Related Complications

It is widely perceived that YOPD patients have an excellent response to L-DOPA treatment, but that this is marred by the early and severe development of treatment related dyskinesias and motor complications (Table 2-6) (Granerus 1979; Pederzoli, Girotti *et al.* 1983; de Jong, Meerwaldt *et al.* 1987; Gershanik and Leist 1987; Quinn, Critchley *et al.* 1987; Gibb and Lees 1988; Giovannini, Piccolo *et al.* 1991; Kostic, Przedborski *et al.* 1991; Hely, Morris *et al.* 1995).

However, studies comparing differences in YOPD and LOPD treatment response are confounded by the widespread practice of delaying L-DOPA treatment in YOPD patients, differences in total L-DOPA dosage and the use of concurrent dopamine agonists. In an attempt to overcome this Kostic and colleagues carried out a carefully matched study of YOPD (onset between 21- 40 years) and LOPD (onset > 40 years) ; matched for gender, duration of disease, mode of onset, Hoehn and Yahr stage, duration of treatment and dose of L-DOPA (Kostic, Przedborski *et al.* 1991). Twenty five patients were identified in each group. The study showed a significantly higher frequency of both dyskinesias and response fluctuations in the YOPD group as compared to the LOPD group. The YOPD group developed complications substantially earlier than patients with LOPD, however the severity of dyskinesia was not significantly different between the two groups.

A further population based study and meta analysis showed a higher 5-year dyskinesia incidence (i.e. in patients who had been on L-dopa for five years) with younger age at onset but did not have any patients with onset before age 40 years and included any appearance of dyskinesia, whether reversible or not on manipulation of medication (Ahlskog and Muenter 2001; Kumar, Van Gerpen *et al.* 2005). Fifty per cent of patients with disease onset between 40-59 years had dyskinesia within 5 years of starting L DOPA, and only 16% of those with onset over 70 years (40% with onset 40-49, 53%

with onset 50-59, 26% with onset 60-69, 16% with onset 70-70 and 14% with onset 80-89 years).

Table 2-6 : Dyskinesia and Motor Fluctuations

Study	*YOPD/ LOPD*	*AAO YOPD*	*Source of Patients*	*Dyskinesia YOPD*	*Dyskinesia LOPD*	Fluctuations YOPD	Fluctuations LOPD
Yokoshi (Yokochi M 1981)	32/-	<40		32%			
Quinn (Quinn, Critchley *et al.* 1987)	56/-	<40	Clinic	55% at 1 y 100% at 6 y			
Perderzoli (Pederzoli, Girotti *et al.* 1983)				Increased			
Tanner (Tanner CM 1985)				91%			
Gibb (Gibb and Lees 1988)	46 / 52	<45	Clinic	91%			
Gershanik (Gershanik and Leist 1987)				75%			
Kostic (Kostic, Przedborski *et al.* 1991)	25 / 25			72% at 3 y*	28% at 3 y	64% 3 y**	28% at 3 y
Hely (Hely, Morris *et al.* 1995)	90 / 33	<70	Sydney Multicentre trial (referral)	No differences			
Barbeau (Barbeau and Pourcher 1982)				42% at 2 y		35% at 2 y	

Abbreviations: YOPD = young onset Parkinson's disease, LOPD = later onset Parkinson's disease, y = years

* p-value for difference =0.002

** p-value for difference=0.01

The available evidence based on clinic series suggests that patients with YOPD develop dyskinesias earlier than LOPD patients but the impact on quality of life has yet to be clarified.

2.11 Familial Aggregation

Twin studies have been influential in evaluating the genetic contribution to the pathogenesis of PD. Low PD concordance in monozygotic/dizygotic twin studies have leant support to the idea that late onset PD is not hereditary (Tanner, Ottman *et al.* 1999; Wirdefeldt, Gatz *et al.* 2004). The situation differs in YOPD. In PD diagnosed under the age of 50 the monozygotic concordance was 1.0 based on only 4 twin pairs compared with 0.16 in twelve dizygotic twin pairs (Tanner, Ottman *et al.* 1999). This strongly indicates that genetic influences are important in YOPD although this is based on small numbers. In both the monozygotic and dizygotic pairs the interval to diagnosis of the second twin was similar, and no statistically significant difference in mean interval to diagnosis was reported when stratified for age at diagnosis. However, in general terms twin studies and first degree relative studies have a limited power to detect the effects of genes of low penetrance which may act differently in young onset and late onset disease (Johnson, Hodge *et al.* 1990).

The advantages of extended genealogy were used in a study of familial recurrence of PD in the Icelandic population (Sveinbjornsdottir, Hicks *et al.* 2000). Twenty percent of the patients in the study on whom onset data were available were classed as YOPD, but attempts to cluster these patients into pedigrees did not show a highly penetrant Mendelian pattern of inheritance, although patients with PD were more related to each other than the controls. A number of studies have suggested a higher incidence of familial occurrence of PD in patients with younger onset disease compared to older onset although a few have failed to confirm this (Mjones 1949; Martin, Young *et al.* 1973; Yokochi, Narabayashi *et al.* 1984; Quinn, Critchley *et al.* 1987; Stern, Marder *et al.* 1993; Payami, Zareparsi *et al.* 2002; Marder, Levy *et al.* 2003; Rocca, McDonnell *et al.* 2004) . The Mayo Clinic study showed that by using the higher age at onset of 66 years relatives of YOPD had a relative risk of 2.62 of developing PD compared to relatives of controls whereas those of LOPD (onset >66) had a similar risk of familial recurrence to

the general population (Rocca, McDonnell *et al.* 2004). Interestingly, analysis in the same study using onset at 50 years as a cut off showed a relative risk of 3.03 for relatives of YOPD compared to 1.62 for LOPD. This highlights the importance of defining and standardizing the age definition for YOPD and LOPD groups.

It is important to note the potential bias in comparing familial aggregation in YOPD and LOPD. It may be harder to obtain accurate detailed information in relatives of LOPD as the family members may be deceased and the diagnosis may have been incorrect or kept quiet from family members as seems to be more the case in older generations. In younger patients there is more likelihood that relatives would be alive and available for direct interrogation of symptoms. This may lead to an underestimation of familial occurrence of PD in older patients.

Overall there is a suggestion that familial recurrence is higher in YOPD than LOPD and this varies with the age definition used.

2.12 Difficulties in comparing current evidence

Most conventional population based prevalence studies of PD describe patients based on their age at ascertainment rather than their age at onset. Most incidence studies, while collecting accurate data on age of onset, only identify small numbers of patients with YOPD. Many of the studies on which observations about YOPD are made are based on highly selected specialty clinic based populations. Differences in referral pattern of YOPD and LOPD patients to specialist services may confound observations in those studies based on specialty clinics populations which appear to be the majority contribution to the current evidence base. This is further compounded by misdiagnosis rates within the community. A community based study performed in London UK, suggested, surprisingly, that atypical patients were less likely to be referred to secondary care and that twenty percent of patients with PD who had already come to medical attention had not been diagnosed as such. On review of the initial diagnosis 15% diagnosed with PD did not fulfill strict clinical criteria for PD (Schrag, Ben-Shlomo *et al.* 2002). In addition, variation in methodology causes difficulty in comparing data from different studies, such as inclusion/ diagnostic criteria, age definitions and disability

measures. To overcome difficulties in the future we believe standardised population based studies are essential.

2.13 Conclusions

The available evidence suggests that, compared with LOPD, patients with YOPD are more likely to a) show slower disease progression , b) develop dystonia at onset, c) develop early dyskinesias in response to L-DOPA treatment, d) have a concordant family history , but less likely to a) develop gait disturbance as an early clinical feature, b) have neuro-psychiatric and cognitive involvement. However many of the available studies are based on age at ascertainment rather than their age at onset, involve small numbers of patients , include highly selected specialty clinic based populations and are subject to variation in methodology which all cause difficulty in comparison across studies and introduce bias at ascertainment. Another source of bias related to the way in which the articles were found. The search strategy was limited to the Ovid Medline databases and only articles published in the English language. A better method would have been to include databases in EMBASE as the journals in these two database sources do not generally overlap and articles may have been missed. Limiting articles to the English language obviously introduces further bias.

The identification of Mendelian PD genes has led to a critical re-evaluation of the concept of PD, and raised the possibility that different pathologies and aetiologies underlie the clinical concept of PD. YOPD comprises a heterogeneous group of patients. It is likely that a subset of YOPD have a different disease based on genetic aetiology and pathology but currently there is not enough evidence in the reported literature to differentiate these subgroups and there is little evidence to suggest that "non- familial" cases of PD without a known genetic mutation are patho-physiologically different to typical LOPD. The description of genes responsible for autosomal recessive parkinsonism and the identification of some cases of genetic autosomal recessive parkinsonism among YOPD case series raises the possibility of dissecting the heterogeneity of PD on a genetic basis. Ultimately this may lead to a more directly patient-centred approach to the management of PD, with specific advice on familial risk, prognosis, likelihood of disease related complications and appropriate disease modifying therapies based on genetic background and age at onset.

Reviewing the published data have illustrated a clear need for large scale standardised population based case control studies of YOPD and LOPD. This is highlighted by the variation in methodologies leading to difficulties in comparisons between published studies.

Some of the points suggested by Twelves at al (Twelves, Perkins *et al.* 2003) to improve the quality and consistency of future incidence studies of PD can clearly be applied to future case control studies investigating features of YOPD, and these include 1) as many of the possible cases as possible should be seen by an expert in movement disorders, 2) cases should be defined by a specific symptom onset rather than date of diagnosis, 3) clear and consistent inclusion and exclusion criteria should be applied, and 4) ideally there should be some follow up to give information to support the diagnosis of PD as per Queen Square Brain Bank Criteria and to assess for symptoms suggestive of a Parkinsonian plus syndrome.

Chapter 3 Methods

3.1 Overall Study Design

The work in this thesis comprises two main parts:

1. A prevalence study of Parkinson's disease in Cardiff analyzed by age at onset
2. A population based case control study of early compared to late onset Parkinson's disease

The prevalence study used primary care as the main ascertainment source supplemented by secondary care resources. This provided a population based pool of Parkinson's disease (PD) patients by age at onset for the case control study. As the numbers of early onset patients was anticipated to be small, supplementary ascertainment of cases was made from secondary care sources outside Cardiff. These supplementary cases were used for the second part of the study and did not form part of prevalence study.
Data were collected on symptom onset, progression, treatment response and related complications, cognitive function and non-motor symptoms.

The data collected will have an immediate and direct impact on the care of patients with PD providing guidance on treatment and help plan service provision.

3.2 Sample Size and Power Calculation

Cardiff has a population of 340,000 and an estimated target pool of 571 patients with PD (previous UK prevalence estimate 168/100,000 (Schrag, Ben-Shlomo *et al.* 2000), of whom approximately 86 (6.6%) will have an age at onset of less than 55 years. In calculating sample size, we assumed a 60% recruitment rate. Therefore, we anticipated recruiting 343 PD patients in Cardiff, of whom a minimum of 52 will have an age at onset of less than 55. The secondary care cases of YOPD were established from the rest of Wales using referrals from physicians (neurologists and geriatricians) running PD clinics and PD nurse specialists. We estimated 40% recruitment and identification of further 151 YOPD patients. Using these conservative figures for case ascertainment, we aimed to recruit a minimum of 203 patients with an age on onset of less than 55 years.

The local series was used to validate the larger series, i.e. to ascertain if there were systematic differences in the primary and secondary care cases.
Power calculations were made using an on-line power calculator (http://www.stat.uiowa.edu/~rlenth/Power/index.html). For a disease feature which occurs in 10% of patients, this sample size (around 200) would have around 80% power of detecting a twofold increase in frequency (20%) with significance set at the 5% level with a 1:1 ratio of young and late onset patients.

3.3 Unique Study Number

Each patient was allocated a unique seven digit study number. This consisted of three parts:

- the first three digits related to the GP practice code (see appendix Table 1)
- the middle digit related to case/control status ie PD case - 1, GP identified control - 2, case nominated control - 3 . The control data do not form part of this thesis.
- the final three digits made up a unique patient code which is generated serially.

For those patients identified via the GP searches, these study codes were assigned once the unique list was compiled from the two independent electronic searches. For those patients referred by secondary care, the study number was assigned before sending out the basic screening questionnaire.
The GP generated patients were assigned their study numbers before case notes were reviewed. This meant that the numbers of patients excluded following case note review and GP screen could be documented as well as the reasons for exclusion. These data were needed for the prevalence analysis.

3.3.1 GP Study Codes

Cardiff Practices

There are 54 functioning GP practices in Cardiff. These were assigned practice codes from 101 to 154 in the same order as they were listed according to their Local Health Board Code.

Practices Outside Cardiff but within Wales

There were eight divisions of study code that were available (2** to 8**) but twenty one Unitary Authorities outside Cardiff, so the Unitary Authorities were grouped according to geographical area. Some consideration had to be taken into account of number of practices within each group as each study code division could only contain a maximum of 99 practices (eg 201 to 299). Therefore, some of the areas with smaller number of practices had to be grouped together, rather than those with geographical proximity.

Practices outside Wales

Any practice outside Wales from which a referred case was registered was given a practice code of 999.

3.4 Prevalence Study

The aim of this part of the study was to estimate the prevalence of PD in a defined geographical area of Cardiff in South Wales. In addition to providing information on the crude and age sex adjusted prevalence rates of PD in Cardiff, information on disease onset was collected, providing an estimate of YOPD prevalence.

3.4.1 Pilot GP searches

In order to find the most effective search strategy for searching GP databases, a pilot study was initiated. This was carried out in three GP practices in Cardiff which varied in size and level of coding accuracy. All Cardiff GP practices used the 5-byte version 2 Read Code edition. The Read Code was used to identify patients with PD based on individual symptoms and examination findings and also on diagnostic terms. The medication section was also examined to identify those used in PD.

Search Terms Used

Three main categories of search terms were used and the number of cases found with each were compared when terms were use singly and in combination to try and find the most sensitive and specific method of complete capture of all patients with PD within the individual GP computerised databases.

Pilot practice visit

The three pilot practices were visited and each search strategy was run separately and numbers of cases identified were recorded. In Wales, there are very few computing systems used by primary care to store and organise patient data, so the majority of practices would use one of the three most common systems used by our pilot practices. Most of the practices visited used the Vision software which was compatible with the majority of the systems used across Cardiff.

Patient unique data were used to ascertain which cases were identified on more than one list and to see which search strategy or combination of search terms were the most effective at capturing the most cases.

At each practices, the patients case notes from those cases identified via the search strategies were checked for diagnostic accuracy and to establish whether miscoding had occurred.
All pilot practices were visited in autumn 2005.

Ely Bridge Practice

The first pilot search was performed at Ely Bridge Practice. This practice had a total list size of approximately 13,000 and claimed up to date coding and accurate diagnostic labelling and data entry, having taken part in many research projects in Cardiff. The system used here was TOREX.

Roath House Practice

The second pilot practice visit took place at Roath House Practice. This had a total practice list size of approximately 7,200. The system used here was EMIS.

Saltmead Practice

The last pilot practice visit took place at Saltmead Practice. This had a total practice list size of approximately 3,000 and was a single handed practice at this time under considerable pressure due to staff shortages. The system used here was GANYMEDE.

Pilot Search Results

Table 3-1 : Results from pilot search strategies from three Cardiff GP practices

SEARCH TERM	*Read code*	*Number of cases identified*	*True PD cases using case notes for verification*
Parkinson's disease	F12	29	25
Parkinson's disease and below	F12 – F12z	35	26
- Paralysis agitans	F120	0	0
- Parkinsonism 2ry to drugs	F121	1	0
- Malignant neuroleptic syndrome	F122	0	0
- Post encephalitic parkinsonism	F123	0	0
- 2ry parkinsonism due to other external agents	F12w	0	0
- 2ry parkinsonism, unspecified	F12x	1	0
- Parkinson's disease, NOS	F12z	7	1
History – difficulty walking	N097	21	0
History – difficulty walking NOS	N097z	0	0
O/E muscle rigid cogwheel	2944	1	0
O/E Parkinsonian tremor	297A	2	0
O/E Parkinsonian flexion posture	2987	0	0
O/E festination Parkinson gait	2994	0	0
Extrapyramidal movements	29M	0	0
Other extrapyramidal disease and abnormal movement disorders	F13	0	0
Parkinsonism and orthostatic hypotension	F1303	0	0
Progressive supranuclear ophthalmoplegia	F1304	0	0
Lewy Body disease	F116	0	0
Multi system atrophy	F174	0	0
Restless leg syndrome		55	0
Other basal ganglia degenerative disease		0	0
History – has a tremor	1B22	81	0
Tremor NOS	R0103	76	0
O/E fine tremor	2975	3	0
Involuntary movements NOS	2972	7	0
Senile tremor	R20	1	0
Benign Essential tremor	F1310	4	0
Familial tremor	F1311	0	0
Drug induced tremor	F1312	0	0
Essential and other specified forms of tremor NOS	F131z	3	0
Parkinsonian dopaminergic drug	dq	58	30
Parkinsonian anticholinergic drug	dv	54	0
Modafinil	dzl	5	0

Table 3-1 shows the number of cases identified by each individual search term for the three pilot practice visits.

3.4.2 Refinement of Search Strategy Following Pilot Visits

Using the PD and below strategy found one extra case in Ely Bridge as compared to searching for PD alone. Searching on prescription codes identified six cases more than the PD and below search. In Roath House, using the PD and below search did not identify any additional cases, neither did the prescription search, although two cases were identified on the diagnostic search who were not on medication.

Following the pilot visits, it was concluded that a search strategy using "tremor" and "any tremor symptom" yielded a large number of patients who did not have PD. It is possible that some patients with tremor had undiagnosed PD but it was not possible to devote time to screen such a large number by examination to identify those patients with PD. Our prevalence estimate was based on medically diagnosed cases only. The terms "tremor" and "tremor symptom" were therefore removed from the diagnostic terms part of the final search strategy.

It was found that on the whole patients who were diagnosed as having PD were coded for one of the diagnostic codes present in the F12 and hierarchical terms.

If patients had been miscoded for diagnosis, and were started on dopaminergic medication, it was possible to identify them via their prescription records. It was best to search for all previous and current prescriptions and to review the medical case notes in conjunction to verify the diagnosis on available information. Some patients were prescribed dopaminergic drugs for conditions other than PD such as restless leg syndrome and prolactinomas. These were very easily identified on either reviewing the electronic code assigned to these patients or on reviewing the hand written case notes.

It was found that the majority of patients that were prescribed anticholinergic medication suffered bladder problems and not PD or tremor. If the patient had concomitant bladder problems and PD, they were invariably prescribed a dopaminergic agent in conjunction.

The anticholinergic group of medications was therefore removed from the medication search term list in the final search strategy.

Some patients were on certain dopaminergic drugs for conditions other than PD. For example bromocriptine is very rarely, if ever, used as a dopamine agonist in PD. Its use in PD has largely been superseded by newer agents such as ropinirole and pramipexole. However, some practices still use bromocriptine to stop lactation in women after termination of pregnancy or in mastitis. Therefore bromocritptine was removed from the dopaminergic group in the medication part of the search strategy.

Amantadine may be used in PD patients when motor complications of L-DOPA use arise and so these patients are usually on combination of dopaminergic drugs. It is not used in isolation in PD patients. However, it is sometime prescribed in isolation to patients with Multiple Sclerosis (MS) to help with fatigue. A patient with MS was identified using Amantadine as part of the search strategy. Those patients with PD on Amantadine would be identified via the search on the other dopaminergic drugs. Therefore Amantadine was removed from the dopaminergic group in the medication part of the search strategy.

Whilst reviewing case notes from every case identified from the search strategies, it became clear that a significant proportion of patients appeared to be miscoded. A patient with Wolf Parkinson White syndrome, a cardiological condition in which conduction abnormality presents in young adults or teenagers, was identified via the search terms piloted. There may have been some confusion with the "Parkinson" part of the syndromic name and this may have been manually coded as Parkinson's disease. In any case, this highlighted the importance of using the electronic search strategies as an initial screen to identify potential cases, and then to verify the diagnosis further by reviewing in detail the medical cases notes. This also gave the opportunity to obtain detailed information on onset age and symptom retrospectively from contemporaneous medical notes, which we assume to be accurate as these are recorded in real time.

The final search strategy was adopted to generate two separate lists generated from the following terms:

1. Diagnostic terms – Parkinson's disease and subgroups (F12-F12z)
2. Medication prescription terms – dopaminergic drugs (dq...) excluding Bromocriptine (dq5..) and Amantadine (dq4..).

3.4.3 GP contact

The heads of all 54 practices were contacted in September 2006 by letter explaining the purpose of the study. This initial contact was followed by e-mail addressed to the practice manager outlining their proposed involvement. If a positive response was received, a telephone call was made to book a practice visit. Those practices who did not respond after 6 weeks were contacted again by e-mail and after a further 3 weeks were contacted by telephone directly. Those practices that declined to participate were not contacted again.

3.4.4 GP visit protocol

Once a mutually convenient appointment was arranged, both myself (MW) and the Project Administrator (COL) visited the practice. Two independent lists were generated by performing two queries from the population list of all currently alive permanently registered patients.

The first list (diagnostic search) consists of all patients who are coded or ever been coded for the hierarchical Read codes F12 to F12z from the 5-byte version 2 Read Code directory. These are summarised in Appendix table 3.

The second list (drug search) was generated by running a query from the entire database of current permanently registered patients who have ever been on or are currently on any of the drugs listed in the group CNS drugs- parkinsonism dopaminergic drugs (dq...) excluding amantadine (dq4..) and bromocriptine (dq5..). These are listed in Appendix tables 4. If the practice could not search by Read code, they were asked to search by drug group, failing that to search by each individual drug name.

Once both lists were generated, duplicates were eliminated and a unique list assembled. These patients were assigned unique study codes and their anonymised details were entered into the Preadmin database. No personalized data left the practices.

MW would personally screen through patient notes (usually both electronic and paper) of those on this list. MW would first determine whether or not the patient had Idiopathic Parkinson's disease by reviewing details on symptoms and response to treatment, and secondly record details of symptom onset or when the diagnosis was first coded if this information was not clearly available. Patients with alternative diagnoses were eliminated and the final list was handed to the GP who was asked to exclude patients in whom it was felt inappropriate to contact (for example if they were terminally ill, demented or mentally ill) or if they did not have PD. The practice was contacted a week after the initial visit to obtain this information and this was directly entered into the Preadmin database using the appropriate study code identifier.

After this final screen was completed the practice sent out a postal pack (postal pack 1) which included an invitation letter from the GP, information about the study and a Basic Screening Questionnaire (BSQ) to the potentially eligible patients. This was used to collect information on diagnostic questions based on the Queen Square Brain Bank criteria for diagnosis of Parkinson's disease and more importantly, information on age at symptom onset as well as seeking written consent for further participation in the project and giving access to their medical records. If no response was received after three weeks of the original invitation, the practice was asked to send a reminder letter to those who had not replied and then again at six weeks if still no response was received. These patients were identified only by their study code number (practice code and patient code) and details such as date of birth, first four digits of the postcode and gender were used to further verify the identity of each patient until they returned the screening questionnaire with their intent to participate further.

Once the basic screening questionnaire was completed, data from this were entered into the Preadmin database. If it was felt on the basis of the patients' answers on the BSQ (plus the medical notes from both the GP and secondary care if available) that the patient fulfilled the diagnostic criteria for possible PD and they had indicated that they would like to participate further in the project, their details were pulled though to the Main Admin Database and they were sent further correspondence regarding the case control study.

3.4.5 Data extraction proforma

Patient identifiable data were not taken away from the GP practice so anonymised data and numbers within groups were recorded.

The following data were recorded from each GP visit:

- the number of patients generated from the diagnostic code search
- the number of patients generated from the drug search
- the number of patients who were on both lists (duplicates)
- the number of patients who were unique i.e. after duplicates taken away
- the number of patients found on one list and not the other and vice versa
- the number of patients excluded by MW as not having Idiopathic Parkinson's disease after screening the notes
- the number of patients excluded by the GP because they were terminally ill, psychiatrically ill, demented, a temporary resident, not PD or for another reason otherwise specified
- the number of patients remaining who were invited
- the date the invitation letter was sent

A list of all study codes of patients from that practice who were eligible to be invited was generated with the corresponding date of birth, gender and first four digits of the postcode along with data on onset symptoms and dates of diagnosis. Also details of whether the patient had had secondary care contact and who if anyone was responsible for ongoing care of their Parkinson's disease was recorded.

3.4.6 Age at Onset Data

Data on age at onset was carefully and intensively sought out. The date pertaining to the first mention in the GP notes of any symptom relating to the four cardinal motor features of PD (tremor, bradykinesia, rigidity and postural instability) was recorded. If the electronic GP notes were not detailed enough or just mentioned a diagnosis of PD at the start of the electronic record, the paper GP notes were scrutinized to obtain more accurate onset data. Secondary care clinic letters were often scanned in to the GP electronic notes, and these were used as an additional source of information if the GP had not recorded exact details of symptom onset. If the secondary care letters were scanned in to the GP electronic records this was still classed as primary care information.

Where accurate onset data was not available from the GP records, every effort was made to search secondary care notes in the hospital, especially for those prevalent cases that were additionally identified via secondary care sources.

3.4.7 Cross check with secondary care sources

Notes were screened for each patient attending the main secondary care PD Clinic in Cardiff over a 6 month period and the database kept by the PD nurse specialist serving Cardiff was utilised. Those living in the Cardiff area were cross-checked against the patients identified via the GP database searches using pseudo-identifiers. Any potential new or missed cases were invited to participate by the patient's secondary care clinician. All physicians and health care professionals involved in the care of patients with PD, including care of the elderly and general physicians and those working at the local day hospital, were contacted to request referral of patients into the study. In addition, Neurology consultants who held general clinics in Cardiff were asked to recruit patients who resided in Cardiff into the study by handing out the screening questionnaire and where available diagnostic records were searched to enable further consultant recruitment of PD patients. A small number of Consultant Neurologists allowed us to use their personal diagnostic databases (in the form of excel spreadsheets) to identify patients with PD and some allowed the electronic hand search of clinic letters held on their secretaries computer hard drives (searching for the term Parkinson's disease or parkinsonism in word documents). Unfortunately there is no comprehensive secondary care electronic diagnostic database that is comparable to that of primary care and so many sources had to be contacted individually. Only patients that were registered with the participating Cardiff general practices were invited for the prevalence study.

3.4.8 Prevalent Cases

Cases were defined as prevalent if they (a) were alive and symptomatic during the period January to December 2006, (b) were registered with a participating practice, (c) had been diagnosed as having PD and (d) met the Queen Square Brain Bank criteria at clinic assessment or if the information held in the clinical notes were consistent with a diagnosis of PD and without recognised exclusion criteria. In addition, a level of diagnostic certainty was applied according to the diagnostic information available.

3.4.9 Statistical method

Data were stored using Access (Microsoft), and analysed using STATA 9 (StataCorp). Crude prevalence rates and 95% confidence intervals were calculated using the Poisson distribution. We calculated age and sex specific rates and standardised these to the 1997 England and Wales population (taken from the Office of National Statistics publication) to allow direct comparison with the previous UK prevalence studies. Previous studies were re-analysed to determine age-standardized rates using the same standard population and the results (95% confidence intervals) were displayed on a forest plot. We calculated the between study variation from a mixed effects Poisson model to derive the p-value for heterogeneity. Comparison of differences in groups was made using the Chi-squared distribution and continuous variables using linear regression.

3.5 Clinical Features by Age at Onset Study

3.5.1 Recruitment of Non Prevalent Cases

Additional cases were recruited from secondary care sources from outside the prevalent GPs in Cardiff and from sources outside Cardiff. All hospital physicians and health care professionals who were involved in the care of people with PD were approached about the study. In particular, the regional PD nurse specialists for Cardiff, Swansea, Newport and Bridgend were a significant case referral source. In addition, presentations were given to the regional Parkinson Disease Society Branch meetings about the study and advertising methods of recruitment. In addition, the study was advertised via the PDS newsletter. Patients were able to self refer in to the study by completing the BSQ. Initially, emphasis was placed on recruiting cases with onset below 55 years from non prevalence Cardiff GPs and outside Cardiff referral sources, but in the later stages of the study, all ages of onset were accepted from these sources in order to obtain target numbers for the clinical features study.

3.5.2 First contact with the study group

Once the patient had returned their completed BSQ, met inclusion criteria from initial screening and had indicated they would like to take part in the case control study, they were first contacted by telephone. If cases were unable to attend the clinic in person they

were given the opportunity to provide information on some sections of the assessment via postal questionnaire. During the first telephone contact patients were given a choice of location as to where they could attend the clinical assessment and a clinic date was booked. A summary of what was to be expected at the clinical assessment and estimated duration of the assessment was discussed and the patient had ample opportunity to ask questions at this stage. Once a clinic date was set, Postal Pack 2 (PP2) was sent out.

3.5.3 Postal Pack 2

Postal Pack 2 (PP2) contained the full Patient Information Sheet (PIS), two copies of the Consent forms, the Life History Questionnaire (LHQ) along with a letter confirming the clinical date, time and location. The patients were asked to read through the PIS in order to discuss any queries in person at the time of the clinical assessment before signing the consent forms. Patients participating by questionnaire only had the opportunity of discussing issues for clarification over the phone, by letter or via e-mail. A stamped addressed envelope was sent with PP2 so that the completed questionnaire could be returned prior to the clinical assessment. The life history questionnaire contained questions concerning early life housing, water supply and exposure to pets, smoking and alcohol consumption, physical exercise in school, occupational history and exposure, past medical history and incorporated the SF-36 v2 (Ware and Sherbourne 1992; Jenkinson, Stewart-Brown *et al.* 1999), (a generic quality of life scale), and the Epworth Sleepiness Scale designed to investigate sleep dysfunction, an important non-motor symptom of PD (Johns 1991). Also obtained was information on consanguinity, place of birth and ethnic origin as well as whether family members suffered from PD or tremor. It is envisaged that this environmental, quality of life and family history data will be analysed following completion of collection of group matched control data and are not reported in this thesis.

3.5.4 Clinical Assessment

On the day of the clinical assessment patients were asked to continue their normal medication and they were assessed in a practically defined "on" motor state. A standardised clinical assessment protocol was followed for each assessment.

Consent

Firstly, the PIS and consent forms were discussed and the opportunity was given for patients and their carers to ask questions. The consent forms were signed by the patients following this discussion and countersigned by the researcher.

History

Details about handedness and referral source were initially recorded and then a detailed freehand clinical history was taken. Questions from a checklist of exclusion criteria were asked. These were taken from the Queen Square Brain Bank Diagnostic Criteria for Idiopathic Parkinson's disease. Standardised questions on dystonia, hallucinations and sleep benefit were incorporated into the history taking. Details on PD medication were then recorded including drug name, dosage, times taken, and start date. Perceived effectiveness of L-DOPA was scored using the appropriate section of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, Elton *et al.* 1987), a standardised validated rating scale commonly used in the assessment of PD. Also from the UPDRS were questions on the development and presence of motor complications related to L-DOPA use. A detailed family tree was drawn in those cases who reported a family history of PD.

Examination

A standardised examination protocol was followed for each assessment. A detailed neurological examination was performed and elements recorded on a standardised proforma. A video recording was made of the UPDRS motor examination and hand writing ability of each patient and the scores for each individual section recorded.
Two further validated standardised scales were used. The thirty point Mini Mental State Examination (MMSE) (Folstein, Folstein *et al.* 1975) was administered by the researcher along with the Lang and Fahn Activities of Living Dyskinesia Quality of Life Scale (2001). The patient was then asked to complete the PDQ-39 (Peto, Jenkinson *et al.* 1995), a disease specific quality of life questionnaire and the Beck's Depression Inventory (Beck, Ward *et al.* 1961).

3.5.5 Postal Questionnaires following Clinic

If the patient had indicated that dyskinesias were present during the clinical assessment, they were asked to fill out a three day patient home diary to record their motor state at half hour intervals during this period. A stamped addressed envelope was provided for the patient to send this back to the study group once completed.

In addition, every participant was sent a Family History Questionnaire. This requested details on every first and second degree relative including screening questions to determine whether any of these relatives had PD, age at onset and current age. The data from the family history questions are not discussed in this thesis.

3.5.6 Drug Information

Information regarding medication doses and start times were taken at the clinical assessment. Supplementary information was requested from GP electronic records and was sent to us as printouts from the appropriate GP surgery electronic database after the patient attended for clinical assessment.

Analysis using start dates for treatment duration used the dates taken from the clinic assessment. If this date was missing, the GP data were used. However, in a small number of cases the electronic records stated medications were started after the clinic date but patients were clearly on the medication at the time of assessment. In these instances the start date was estimated as a year from diagnosis.

3.5.7 Data Entry

Once data were collected and recorded on the clinic proformas, this was entered on to the Main Admin Database by the research doctor, the research administrator and, mainly, trained medical students.

3.5.8 Data analysis

Data were analysed using STATA 9 (StataCorp). For the clinical features study, Chi-squared tests were used to compare heterogeneity and trend, and means were compared using the unpaired t-test. The effect of age at onset was studied in two ways: either in four groups with onset <45, 45-54, 55-64 and ≥65 years, or in two groups with age above

and below 45 years. This was to see whether associations show a dose-response effect with age or whether there is a bi-modal distribution with differences only seen in the youngest group. Multiple regression analyses were used to assess the confounding effects of both disease and treatment duration.

3.6 Database Design

The database was designed in collaboration with Peter Shiarly (Department of Social Medicine at Bristol University).
There were two linked databases allowing for the initial anonymous data entry for the prevalence study (Preadmin Database) then linking to the main project database which required patient identifiers and consent for coordinating the administration of the project. It was possible to extract all data in an anonymised format for analysis. The database was written in Microsoft Access and largely comprised numerical codes for categorical data, including flag fields for subject status.

3.6.1 Preadmin Database

This was designed to store all data collected from the prevalence study and so was designed to contain only anonymised data.

A section relating to GP practice visit details contained fields for dates of each part of the visit protocol. This facilitated the administration process of the project allowing queries to be generated to aid the smooth running of the GP protocol whereby several practices may have been in different stages at any given time. Coordination of the practice visits was possible through recording dates and details of practice visits, when initial letters were sent inviting patients and when reminders were due. This all had to be conveyed to the individual practice on an anonymised basis at the correct intervals.

Also entered in this section were data collected through the ascertainment process, which allowed us to look at case numbers generated from each individual search strategy and exclusions.

Anonymised data from any potential patient identified or referred into the study were entered into the Preadmin database. Anonymous data were collected from each subject including date of birth, gender and partial postcode. Each subject was assigned a unique study code under which data were entered into the database. The GP practice at which the subject was registered formed the first part of this study code.

Data gathered at the GP visit were entered, the patients' response to being invited into the study, along with data from the basic screening questionnaire when this was completed by the patient. Those patients who consented to taking part in the main study and who were eligible by diagnostic criteria were pulled through to the Main Admin Database and were sent further instructions for continued participation.

3.6.2 Main Admin Database

This contained identifiable patient details to help the administration of the project, such as generating clinic and thank you letters, along with monitoring the patients' journey through the numerous steps involved in the data collection process. All data collected after the basic screening questionnaire were entered on to this database, and all patients seen in clinic and invited to participate via questionnaire only were captured here. Dates at which patients were seen in clinic, sent various questionnaires and when these were returned were also recorded.

3.7 Specific Ethical considerations

As the data collected were similar to what may be collected in routine clinical practice, the main ethical considerations arose from how the initial patient contact was made and also concerns about the potential consequences of any genetic analysis. Patient confidentiality and data protection issues were also a concern.

Particular issues involved the following points:
In the prevalence study:

- The patients identified via the GP database searches may not have been known by the research team or the department of neurology so had to be approached by their GP directly as the first point of contact to be informed about the study. A

standardised letter was produced which came from the patients' own GP who signed by them personally.

- Once the patients were identified, no identifiable data could be taken out of the practice until the patients had replied to the research team directly giving written consent to be involved in the study. Only anonymous data were taken regarding numbers of patients identified at each stage of the ascertainment protocol, in line with the Data Protection Act.
- Patients could only be contacted by the research team once they had replied directly back to us with their contact details and written signed consent indicating that they were willing to participate in this study.

Secondary care referrals

- Professionals referring patients directly into the study were asked to obtain written signed consent that the patient had agreed to be contacted to receive further information regarding the study. This was achieved via completion of pamphlets or completion of the basic screening questionnaire, both of which request written signed consent from the patient.
- On occasion the study team may have sent out the basic screening questionnaire with a cover letter from the appropriate consultant or PD nurse specialist on their behalf as the first point of contact, after obtaining the appropriate professional's consent and signature on the cover letter.

Presentations at patient group meetings

- At these meetings the project was explained in detail in lay terms and the patients were given the opportunity to ask questions at the time. If they were happy to participate from the information given at the meeting they were handed a basic screening questionnaire at that point.

All patients having filled in the BSQ and having indicated they were agreeable to participate further in the study were sent the full patient information sheet (PIS) and were asked for more detailed written signed consent.

Third party consent

- For those patients who did not have full capacity to give informed consent but where their carers or relatives felt it was in the best interest of the patient to participate in the study, it was possible to obtain assent from the appropriate relative or carer. There was a specific section in the PIS to address this issue.

Implications of genetic testing

- The potential for a diagnostic test to be developed arising from genetic analysis of patients DNA was explicitly explained along with the possible implications of a positive test result.
- Currently there is no cure for PD nor is there any proven neuroprotective agent available and so the development for a preclinical diagnostic test has limited value in PD at this time.

Chapter 4 Prevalence Study of Parkinson's Disease in Cardiff by Age at Onset

4.1 Chapter Summary

Although there have been many previous UK epidemiological studies of PD, none have studied the prevalence of YOPD and several have been limited as discussed in Chapter 1. This chapter describes a community based prevalence study undertaken in Cardiff, South Wales, particularly focussing on age at onset. Data on age at onset and onset symptom, as the cases are established prevalent cases, have been collected retrospectively and may not be as accurate as data gathered from an incidence study. However, age at onset data have been obtained from several sources including contemporaneous primary care records, specialist clinic letters and the patients' own recall of events. Age at onset, symptom onset and disease burden on healthcare of PD patients in Cardiff is described. We found the crude prevalence of PD in Cardiff to be 130 per 10^5 (95% CI 117,144) and 142 per 10^5 (95% CI 128,156) when standardised to the 1997 population of England and Wales. The prevalence of YOPD (onset <50) was 6.2 per 10^5 accounting for 5.4% of the prevalent cases. Neurologists were responsible for diagnosing 44% and following up 17% of the total prevalent group, but diagnosing 90% and following up 56% of those with onset before 45 years. Overall, the majority of follow up care was provided by the geriatrician led clinic (63%). Comparison to previous UK studies showed our prevalence rates to be close to the weighted average. There was no obvious temporal trend in prevalence rates over the past 42 years in the UK.

4.2 Introduction

Data from a community-based prevalence study of PD in Cardiff, South Wales are presented. The aims of this study were to 1) add further information on the potential geographical and temporal variation of PD prevalence across the UK, 2) specifically examine what proportion of prevalent cases had young onset disease, 3) examine how age at onset influences source of health care and 4) undertake a meta-analysis of all published UK prevalence studies.

Methods are described in Chapter 3. This study has a number of strengths, following the desirable features described by Twelves and colleagues in their review of UK incidence studies : 1) a large population size (>250,000), 2) multiple source case ascertainment, 3) attempted review of all cases by movement disorders specialist, 4) definition of specific symptom onset date as well as diagnosis date, 5) clearly defined inclusion criteria, 6) use of Queen Square Brain Bank Diagnostic Criteria in clinic assessment (although this was limited in application to case note review), and 7) reporting of standardised age strata and confidence intervals.

4.3 Results

4.3.1 Practice participation

Forty-five out of 54 (83%) eligible practices participated in this study. This provided a population denominator of 292,637, representing 96% of the Cardiff population. Although only 83% of practices participated, it was possible to capture practices serving 96% of Cardiff as smaller single handed practices were more likely to decline participation.

4.3.2 Electronic database searches and notes review in primary care

The diagnostic search (Read Code F12-F12z) generated 412 case records and the prescription search (Dopaminergic Drugs excluding Bromocriptine and Amantadine) provided 633 case records. This gave a total of 731 unique individual potential cases (see Figure 1). Two hundred and ten patients were identified as having been prescribed dopaminergic agents for an alternative diagnosis. An additional 96 patients were identified with parkinsonism due to a secondary cause under this search strategy: 42 vascular parkinsonism, 32 drug induced parkinsonism, 13 Lewy Body Dementia, 2 dementia with parkinsonism, 3 Multiple System Atrophy, 2 Neuroleptic Malignant Syndrome, 1 Neurosyphilis, and 1 Progressive Supranuclear Palsy. A further 72 patients did not have PD on case record review: 26 patients were miscoded and did not have a movement disorder, 35 had essential tremor (but were identified via the drug search because they had undergone a trial of L DOPA) and 11 further patients were initially diagnosed and coded as PD but the diagnosis was revised at specialist review, and the Read code had not been updated.

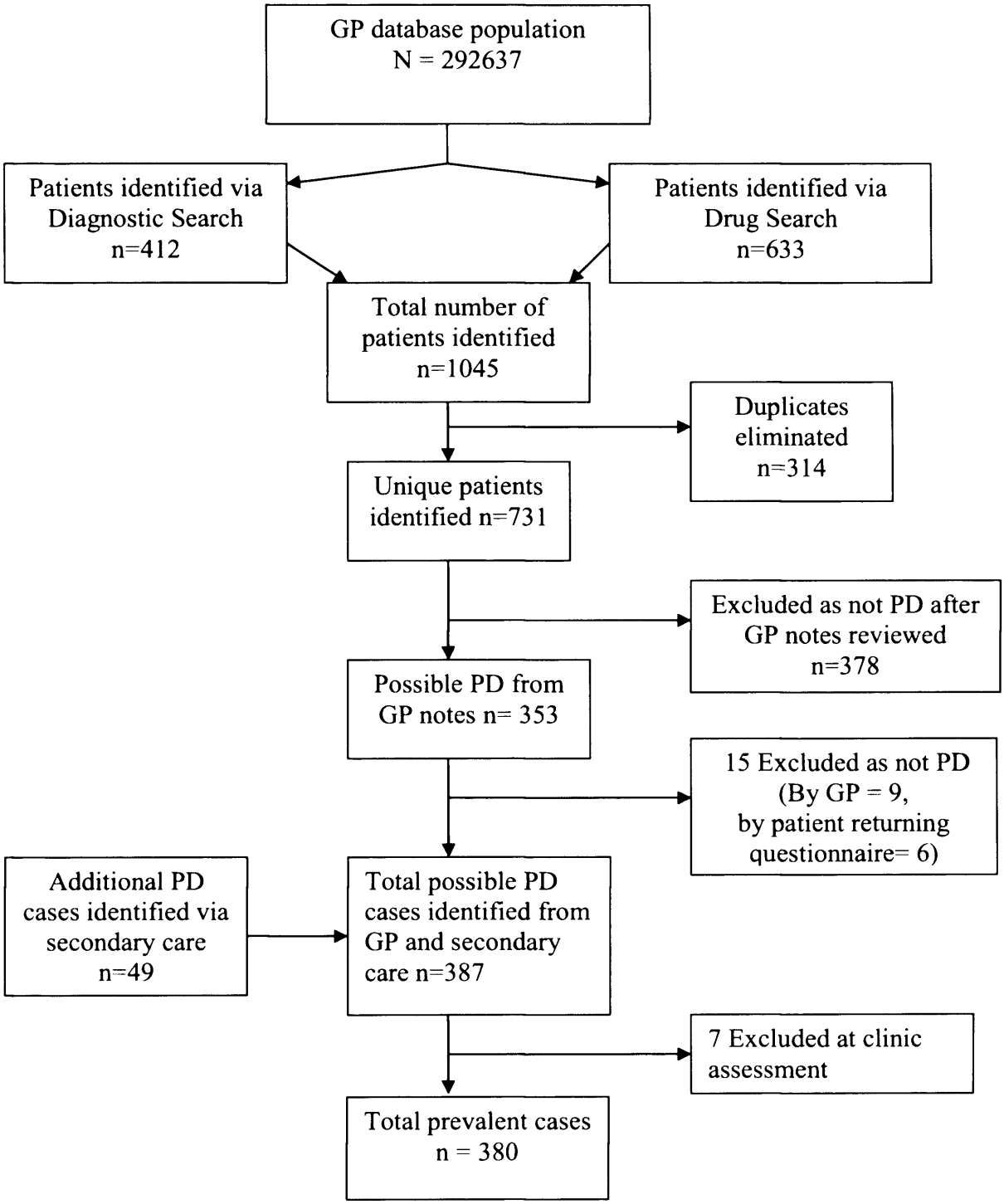
4.3.3 Additional Cases recruited via secondary care sources

In addition, a further 49 cases were identified from sources other than the GP databases. Twenty cases were identified from general neurology clinics, 27 from the geriatrician run PD clinic, 1 self referral and 1 from another source. These cases had been registered with the prevalent general practices but had not already been identified from the GP database search strategies. This resulted in 402 potential cases in total.

4.3.4 Exclusion as not PD

Fifteen patients were excluded before examination as not having PD (9 by general practitioner and 6 by patient stating that they did not have PD). One hundred and thirty two of the 387 potential prevalent cases were examined in clinic (35%) of which 7 additional patients (5%) were excluded as not having PD (including the self-referral case). Only one diagnosis-revised case had not seen a secondary care specialist. This resulted in 380 prevalent cases (182 females, 198 male) of which 168 were identified by more than one referral source.

Figure 1 : Summary of number of cases prevalent during January – December 2006 identified via search GP Database Strategy



4.3.5 Crude and age and sex standardised prevalence

For both men and women, prevalence rates increased with age group, though male rates were greater in all groups. The crude prevalence rate was 130 per 100,000 (95% CI 117, 144) overall; men 134 per 100,000 (95% CI 116, 154) and women 126 per 100,000 (95% CI 108, 145). The age adjusted rates rose to 142 per 100,000 (95% CI 128, 156) overall, and male and female rates increased to 171 (95% CI 147, 195) and 120 (95% CI 103, 138) respectively (see Table 4-1) adjusted to the 1997 population of England and Wales. The male to female age adjusted prevalence rate ratio was 1.43 (95% CI 1.17, 1.76, p=0.001).

Table 4-1 : Age, sex specific and standardised prevalence rates of PD

	Total			Men			Women		
Age (yrs)	PD cases	Population size	Age-specific rates per 100,000	PD cases	Population size	Age-specific rates per 100,000	PD cases	Population size	Age-specific rates per 100,000
0-29	0	122,571	0	0	61,661	0	0	60,910	0
30-39	1	44,399	2.3	0	23,397	0	1	21,002	4.8
40-49	4	40,523	9.9	4	21,429	19	0	19,094	0
50-59	24	32,249	74	14	16,901	83	10	15,348	65
60-69	63	23,155	272	38	11,616	327	25	11,539	217
70-79	129	17,481	738	68	8,193	830	61	9,288	657
>80	159	12,259	1297	74	4,413	1677	85	7,846	1083
Crude rate per 100,000	380	292,637	130	198	147,610	134	182	145,027	126
Age standardized rates per 100,000*	142 (128, 156)			171 (147, 195)			120 (103, 138)		

4.3.6 Diagnostic Certainty

A level of diagnostic certainty was assigned to the prevalent cases depending on the information available. The highest level of certainty applied to those patients seen in the research clinic, meeting Queen Square Brain Bank diagnostic criteria (level 1 - 33% of prevalent cases). The next level of certainty involved contact and diagnosis or

management by a neurologist or PD specialist (level 2 - 52%). Some patients' records indicated that they had been diagnosed and managed entirely in primary care (level 3 – 15%). In total 85% of PD patients, identified in primary care had been seen by a neurologist or PD specialist.

4.3.7 Age at onset

Age at symptom onset was obtained for 336 of the 380 (88%) prevalent cases (Table 4-2). Of this 336 cases, onset data was obtained from contemporaneous primary care records in 325 cases (97%) and from separate secondary care records in 11 cases (3%). The mean age at onset of our cohort was 68.6 years (95% CI 67.5, 69.8). For men, mean age at onset was 67.7 years (95% CI 66.0, 69.3 years) and for women mean age at onset was 69.7 years (95% CI 68.1, 71.4 years). There was a bimodal distribution of age at onset with peaks at 40-44 years and 75-79 years. The average disease duration for the prevalent group was 6.2 years (range 0.7-28.1 years). The YOPD group (onset <45 years) had longer disease duration (11.1 years, 95% CI 7.9, 14.4 years) than the LOPD group (onset ≥ 45 years), (6.0 years, 95% CI 5.4, 6.5) with a significant difference of 5.1 years (95% CI 2.2, 8.0, p=0.0006). Cases who did not attend the research clinic had an older age at onset but similar disease duration (see table 4-3).

Table 4-2 : Age at onset frequency of all prevalent cases where data available from GP and hospital records

Age at onset	Total		Men		Women	
	No (%)	Cumulative frequency (%)	No (%)	Cumulative frequency (%)	No (%)	Cumulative frequency (%)
25-29	1 (0.3)	0.3	1 (0.6)	0.6	0 (0.0)	0
30-34	1 (0.3)	0.6	0 (0.0)	0.6	1 (0.6)	0.6
35-39	1 (0.3)	0.9	0 (0.0)	0.6	1 (0.6)	1.2
40-44	9 (2.7)	3.6	7 (4.0)	4.6	2 (1.3)	2.5
45-49	6 (1.8)	5.4	4 (2.3)	6.9	2 (1.3)	3.8
50-54	15 (4.5)	9.9	8 (4.5)	11.4	7 (4.4)	8.2
55-59	34 (10)	19.9	18 (10.2)	21.6	16 (10.0)	18.2
60-64	38 (11.3)	31.2	23 (13.1)	34.7	15 (9.4)	27.6
65-69	50 (14.9)	46.1	25 (14.2)	48.9	25 (15.6)	43.2
70-74	73 (21.7)	67.8	40 (22.7)	71.6	33 (20.6)	63.8
75-79	59 (17.6)	85.4	25 (14.2)	85.8	34 (21.2)	85
80-84	36 (10.7)	96.1	20 (11.4)	97.2	16 (10.0)	95.1
>85	13 (3.9)	100	5 (2.8)	100	8 (5.0)	100
Total	336 (100.0)		176 (100.0)		160 (100.0)	

Table 4-3 : Mean age, age at onset and disease duration by gender and whether or not patients were seen in research clinic.

	Age		Age at onset		Disease duration	
	Mean (95%CI)	P value	Mean (95%CI)	P value	Mean (95%CI)	P value
Male	74.0 (72.5, 75.4)	0.03	67.7 (66.0, 69.3)	0.08	6.0 (5.3, 6.8)	0.61
Female	76.1 (74.7, 77.6)		69.7 (68.1, 71.4)		6.3 (5.5, 7.1)	
Seen in clinic	72.2 (70.5, 73.9)	0.0001	65.9 (63.9, 67.9)	0.0006	6.2 (5.3, 7.0)	0.9
Not seen in clinic	76.4 (75.2, 77.6)		70.2 (68.7, 71.6)		6.2 (5.5, 6.9)	

4.3.8 Diagnosing and Follow up Care provision

Neurologists were most likely to have made the diagnosis of PD (44%). For YOPD, a neurologist made the diagnosis in 90% of cases ($p<0.001$), though in a substantial number of cases (41%) there was no information available. There was a substantial increase in the rate of GP diagnosis of PD with increasing age at onset (Table 4-4). Overall follow up care was mainly provided by the geriatrician led PD clinic (63%) and neurologists (17%) although again details were not available on follow up care in 39% (Table 4-4).

4.3.9 Misdiagnosis rates amongst those seen in research clinic

Of those patients assessed in the research clinic, 45.5% were under follow up by the movement disorder geriatrician, 22.7% by neurologists, 4.5% by GPs, 1.5% by general geriatricians and 0.8% by general medical physicians. In 7/132 (5.3%) of patients, the diagnosis of PD was revised to an alternative diagnosis at the research clinic - 1 (3.3%) of those followed up by neurologists, 4 (6.7%) of those followed up by the movement disorder geriatrician, 1 (16.7%) of those followed up by GPs and 1 (100%) of those followed up by the general physicians.

Table 4-4 : Distribution of diagnosing and follow-up specialty by age of disease onset

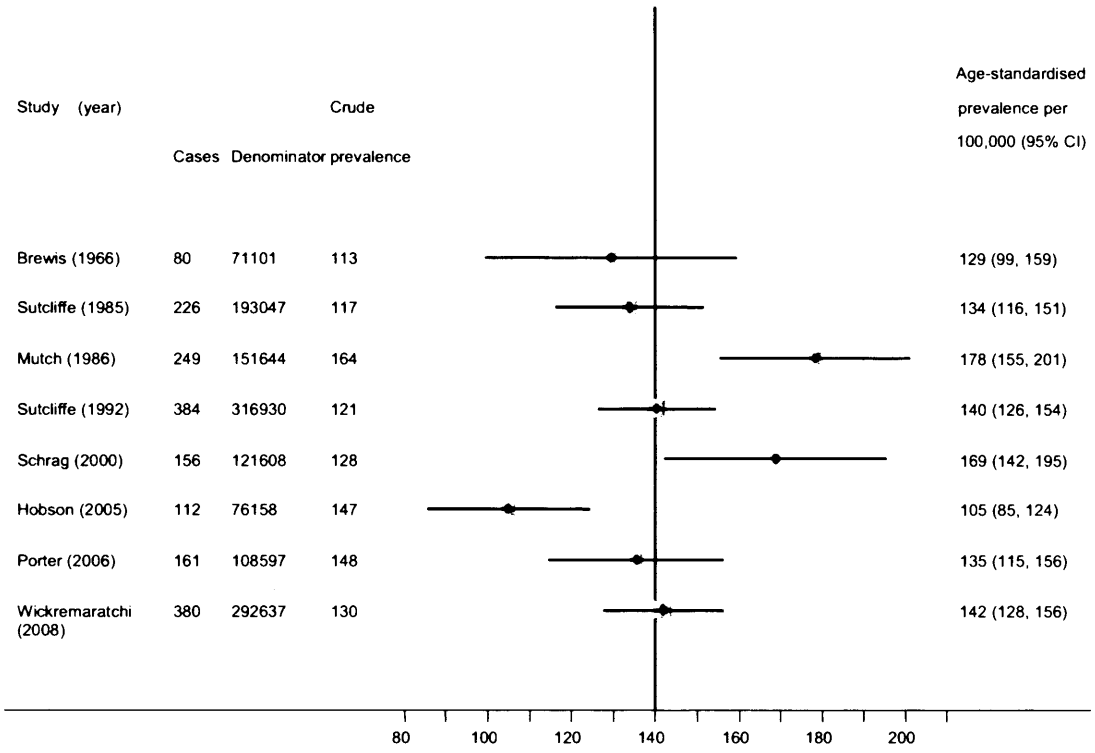
	Whole group n (%)	Onset <45 yrs n (%)	Onset 45-64 yrs n (%)	Onset ≥65yrs N (%)
Diagnosing physician	**n=223**	**n=10**	**n=74**	**N=139**
Neurologist	99 (44)	9 (90)	47 (64)	43 (31)
Movement disorder geriatrician	64 (29)	1 (10)	15 (20)	48 (35)
Geriatrician	15 (7)	0	3 (4)	12 (9)
GP	28 (13)	0	8 (11)	20 (14)
Medics	15 (7)	0	1 (1)	14 (10)
Other	2 (1)	0	0	2 (1)
Follow-up care	**n=231**	**n=9**	**n=70**	**N=152**
Neurologist	40 (17)	5 (56)	21 (30)	14 (9)
Movement disorder geriatrician	146 (63)	4 (44)	40 (57)	102 (68)
Geriatrician	13 (6)	0	2 (3)	11 (7)
GP	28 (12)	0	5 (7)	23 (15)
Medics	3 (1)	0	1 (1.5)	2 (1)
Other	1 (1)	0	1 (1.5)	0

GP = general practitioner
Details on diagnosing physician available on 223 patients ($p<0.001$).
Details on follow up physician available on 231 patients ($p<0.001$).

4.3.10 Comparison with other UK PD Prevalence Studies

A comparison was made of these results with all previously published UK prevalence studies (Figure 2). The crude rates varied from 113 to 164 per 100,000, however after standardization to the 1997 population of England and Wales, this increased to 105 to 178 per 100,000. Our prevalence rate at 142 per 100,000 was very close to the global average but there was evidence of statistical heterogeneity between these standardised rates (p-value for between study heterogeneity =0.0006). There was no obvious temporal trend suggesting that prevalence rates showed no systematic change over the last 42 years.

Figure 2 : Forest plot of age-standardized PD prevalence rates in the United Kingdom (1966-2008)



4.4 Discussion

This prevalence study is one of the largest UK studies using computerized records in primary care and supplemented by secondary care data.

Our data confirm the previously accepted observations that age specific rates increase with age, particularly after age 55 years. In every age band, the age specific rates are higher in men than women as is consistent with incidence data (Wooten, Currie *et al.* 2004). Our male to female prevalence rate ratio of 1.43 (95% CI 1.17, 1.76, p=0.001) is comparable to data from incidence studies (1.9 in a US incidence study, 2.3 (95%CI 1.55-3.28) in a UK incidence study) (Twelves, Perkins *et al.* 2003; Van Den Eeden, Tanner *et al.* 2003; Taylor, Counsell *et al.* 2006). However, one must bear in mind that differential

survival between male and female cases may affect prevalence rates, and so incidence and prevalence gender specific rates may not be strictly comparable. Greater survival of females influence female prevalence rates ie will be higher, whereas incidence rates are not affected by survival. The standardised rates suggest the Cardiff population have a larger proportion of older female residents than the 1997 population of England and Wales used for standardisation. Age at onset was a major focus of this study and relied on contemporaneous primary care records where available, or subsequently from secondary care clinic letters. Nevertheless, age at onset is likely to be less accurate than data derived from incidence studies. The mean age at onset in our prevalent patients was 68.6 years. These estimates are comparable to data from UK and US incidence studies (mean age at diagnosis 70.5 in the US incidence study, mean AAO 67.8, mean age at diagnosis 70.3 in the Cambridge incidence study and mean age at diagnosis 76.1 years in the Aberdeen incidence study) (Van Den Eeden, Tanner *et al.* 2003; Foltynie, Brayne *et al.* 2004; Taylor, Counsell *et al.* 2006). Our data suggest the possibility of a bimodal pattern of age at onset with a peak at 40- 45 and again at 75-79 years, but numbers are very small at the younger onset ages and so this observation could be consistent with chance. It is important to note that previous incidence studies have not shown a significant observation of bimodal age at onset in PD.

The major finding of this study is that the prevalence of PD in Cardiff is similar to other studies in the United Kingdom (at around 140 per 100,000). Although the prevalence of young PD cases is much lower than that for older cases, 5.4% and 31.2% of the total prevalent PD population have their disease onset before 50 years or 65 years of age respectively. Around 1 in 20 PD patients develop disease before the age of 45, normally considered to be a cut-off at which genetic autosomal recessive PD should be considered. Whilst the rate of PD in those whose current age is below 50 in Cardiff is 2.4 per 100,000, the prevalence of those whose disease started before the age of 50 is three times higher at 6.2 per 100,000. These figures equate to approximately 3700 people in the UK currently alive with YOPD and means that YOPD, defined by an age of onset below 50, is at least as common as Motor Neuron Disease, Huntington disease and Progressive Supranuclear Palsy. These data have implications for both genetic testing and the need for greater provision of support for patients in employment.

A period prevalence was given as opposed to a point prevalence. This was because cases had to be identified in the GP practice and only anonymised data could be extracted. In order to provide a point prevalence, identifiable data would be required to check that those cases were resident and alive on the prevalence date. As cases were collected over a period of twelve months it was only possible to provide a period prevalence over this period. Period and point prevalence estimates may not be strictly comparable. Estimates of period prevalence may be higher as they include patients alive and symptomatic over a substantial period who would not have been prevalent if an estimate was taken at the mid point of that period, ie those captured in the latter part of the period would not have been captured on the point prevalent date.

The search strategy used in this study was not designed to identify Parkinson plus syndromes such as Progressive Supranuclear Palsy and Multiple System Atrophy. However, a number of these cases were identified using the codes for Parkinson's disease and below (F12 –F12z). It is important to note that the figures obtained from this study for the Parkinson plus syndromes do not represent the true prevalence of PSP or MSA but are an underestimate as the specific diagnostic codes for the Parkinsonian plus syndromes were not used. Therefore, an estimate was not given for the prevalence of the Parkinson plus syndromes.

This case finding approach highlighted the need for multiple source case ascertainment as relying only on primary care cases alone would have led to missing an additional 13% of potential cases. Also direct assessment of primary care data was essential since 37 cases were miscoded as having PD (11% of total prevalent primary care cases) due to data entry error, or failure to change or remove inapplicable diagnostic codes. The NHS is often cited as a good environment in which to perform epidemiological research because of uniform health care provision and coding, but the degree of miscoding was high when identifying PD patients. Relying solely on GP codes would have led to substantial errors in our prevalence estimates. This suggests that a great deal of caution is needed in relying on non-specialist diagnostic code databases.

The meta-analysis of all UK studies suggests that the prevalence of PD in the UK has been relatively stable over the past 40 years. This is somewhat surprising given the

increase in overall life expectancy and the better management of PD, which would if anything also increase survival and therefore prevalence. There are several possible reasons for this observation. (a) Decline in incidence: As prevalence is a function of incidence and disease survival, assuming that survival has increased then the true incidence may have actually declined over time. This hypothesis is not supported, however, by analysis of the incidence trends from 1976 to 1990 Rochester, Minnesota (Rocca, Bower *et al.* 2001), (b) Greater awareness of other Parkinsonian conditions: Over the last forty years there has been far greater awareness of other conditions such as multiple system atrophy which may be misdiagnosed as PD. Although these conditions contribute at most 10% of all patients with parkinsonism (Schrag, Ben-Shlomo *et al.* 1999), more recent studies are likely to have excluded such cases more thoroughly and this may therefore counterbalance any increase in prevalence due to greater survival. A balancing of the prevalence inflating effects of increased survival with the prevalence diminishing effects of increased diagnostic precision seems the most likely explanation for the stable UK prevalence rate.

It is likely that the heterogeneity between studies can be explained by methodological differences. The study from Aberdeen, with the highest rate, actively searched for cases in nursing homes, which will have an over-representation of PD cases, and may have been overlooked in primary care records (Mutch, Dingwall-Fordyce *et al.* 1986). In a Norwegian study looking at nursing home residents, 5% of residents had PD, nearly 20% of whom were previously undiagnosed (Larsen 1991). In contrast, the study from rural Wales (Hobson JP 1999) had the lowest prevalence rate. This study did not use diagnostic databases but relied on prescription records and referrals possibly leading to under ascertainment of cases. In addition, it is not known whether PD survival is worse in rural as compared to urban areas. However, our data derived from an urban Welsh population compared to the North Wales study, do not support the notion that a rural environment increases the risk of developing PD (Ben-Shlomo 1996).

The UK has a relatively low provision of specialist neurologists in comparison to Western Europe and the USA. Geriatricians, general physicians and general practitioners as well as neurologists diagnose and care for PD patients. In addition, there is a cadre of well-trained geriatricians who have a special interest in movement disorders and are

possibly better suited to the complex multi-faceted needs of elderly patients with PD. Not surprisingly, almost all of the YOPD patients were diagnosed by a neurologist but only one third of later onset patients. Neurologists only looked after around half of the YOPD patients, but few (9%) whose disease started after the age of 65. A substantial minority (15%) of PD patients were followed up solely by their general practitioners. It is harder to know whether follow-up by a general practitioner is desirable but at some stages in the disease this may be appropriate especially for frail elderly patients who have difficulty attending out-patient clinics. Recent national guidelines (Royal College of Physicians 2006) suggest that the diagnosis of PD should always be made by a specialist but this was not the case at the time of our study. The actual proportion diagnosed by a general practitioner is probably an under-estimate as it is likely that GP diagnosis also occurred in cases where a specific diagnosing clinician was not recorded. These results reflect local PD service provision but are likely to be mirrored to some extent through the UK and overseas. Overall diagnostic accuracy among those patients assessed in our research clinic was high with around 95% of patients meeting the Queen Square Brain Bank criteria for PD. We do not know whether this would be true for those patients who did not attend the research clinic or the patients with "tremor" who were not evaluated. A small number of patients carried a diagnostic label of PD, but had alternative diagnoses. Patients under follow-up in neurology clinics were most likely to fulfil diagnostic criteria for PD, based on a small number of re-classified patients. A small number of patients (15%) had been diagnosed and were under follow up with their general practitioner and the diagnostic accuracy in this group is not known.

4.4.1 Limitations

A number of limitations of this study can be identified.

Firstly, a more accurate prevalence estimate could have been obtained from performing a door-to-door survey of households in Cardiff. However, time and financial constraints did not make this a feasible option. In the UK, health care is available to all and free of cost at the point of access. This suggests that primary care records theoretically should represent the health of the whole community assuming those who require medical advice consult their GP. Our prevalence study was designed to identify medically diagnosed cases of PD and not designed to screen and pick up undiagnosed cases in the community

who had not yet sought medical advice. These undiagnosed cases, although contributing to the true prevalence of the disease, have not yet come to medical attention and so have not yet influenced health care burden.

Although a very high rate of participation from primary care practices in Cardiff was obtained, only around a third of all the cases were clinically examined. This introduces problems with diagnostic accuracy especially given the substantial miscoding and misdiagnosis rates discovered in primary care during the course of this study. This highlights the need for supplementing primary care case notes with secondary care records and face to face examination of the patients, to obtain the most accurate diagnostic and case definition data. Secondary care records are filed in primary care notes, allowing assimilation of case data from an expert assessor. It is unfortunate that in today's busy primary care environment difficulties in recording and coding patient consultation data accurately and in sufficient detail exist, as this would be a prime source of epidemiological data captured in real time, and provide a way of retrospectively collecting onset data. Better IT data capture systems could improve this. In order to get the most accurate estimate of disease prevalence multiple sources are needed – some cases are not picked up in primary care alone. If these details were recorded accurately and in enough detail this could provide a way of approximating incidence data retrospectively, obviously not accounting for survival rates.

This study also highlighted limitations of undertaking a prevalence study solely in secondary care. Hospital diagnostic coding information is only kept on those patients who are admitted to hospital and even then the reason for admission may be the sole diagnostic code recorded. In general, PD is a chronic disease which tends to be mainly managed in the outpatient setting. If patients with PD are admitted to hospital it is usually for another reason, and so their diagnosis of PD may not be recorded. Thus current hospital coding records are not an adequate source of diagnostic information on which to base prevalence ascertainment. Only a minority of neurology consultants kept their own diagnostic database. This proved to be a very useful ascertainment resource. However, for the majority of the neurology department, clinic letters stored on hard drives of the individual secretaries had to be hand searched in order to identify those with PD. This proved to be a time consuming exercise that only yielded few additional cases although

the detail of information gathered from this source was far superior to that of primary care records.

Although it was identified at the start of the study that using only primary or only secondary care sources would not provide an accurate prevalence estimate, the individual problems in both primary and secondary care coding systems were not appreciated until the study began. By obtaining as much information from as many sources as possible about the patients' symptoms and disease course, it was possible to overcome some of these problems but this led to an increase in workload that had not been anticipated.

Methodological developments suggest that capture-recapture methods using primary and secondary care data may be useful to estimate the number of missed cases and can be used in sensitivity analyses though they add to the complexity of the study design, statistical methods and ideally require non-anonymised identification. This technique relies on source independence and the randomness of identification of cases from each source (Tilling, Sterne *et al.* 2001). As the diagnosis of PD was confirmed in secondary care in the vast majority of the cases, this implies that there is not true source independence or randomness of identification, as the sources are interlinked.
Due to ethical constraints, it was not possible to take non-anonymised data from the GP practices, thus performing capture-recapture analysis would have been difficult, although we were able to describe how many cases had been identified by more than one ascertainment source. However, this information was not systematically collected.
Although from the primary care records it was suggested that 85% of the prevalent cases had contact with secondary care at some point during their disease course, not all of these patients were identified as being captured via the secondary care referral source in addition to the primary care source. This may have been because these patients had been discharged from active follow up from secondary care as it may have been felt once the diagnosis was confirmed the uncomplicated stable phase of the condition could be managed in primary care, and so the searching of secondary care clinic notes and letters may not have identified these cases. It is also likely that the specific secondary care team was not identified for some patients and therefore these data were missing in our database thus leading to those cases not being identified as coming from secondary care source. It

is possible that incompleteness of the secondary care recruitment has lead to further under estimation of the true prevalence of PD.

This study design only allowed for those cases that were correctly identified and diagnosed as having PD to be included in the prevalence estimate. Due to the misdiagnosis of patients who have already come into contact with medical care but have not been recognised as having PD this has no doubt lead to an under estimation of true PD prevalence. It is possible that some of the patients labelled as Parkinsonian plus syndromes actually may have had PD but these notes were not screened, and these patients were not invited for clinical review. These diagnostic labels are generally applied by specialists rather than primary care physicians, nevertheless this may potentially have been a source of underestimation of the true prevalence of PD, though the suspicion is that the number would be small. Cases with a diagnosis of essential tremor were not invited to be examined due to time constraints, though the previous London study (Schrag A 2000) identified patients with unrecognized tremor dominant PD by screening patients who developed tremor after the age of 50 years. In that study 11 of the 56 patients who had previously been diagnosed to have non-Parkinsonian tremor had probable or possible PD and their inclusion increased the number of PD cases by 7.9%. Due to the time and resource constraints of this study, it was not feasible to screen patients with tremor in every prevalent GP practice, and is likely to have led to an underestimation of true PD prevalence. Although the confidence intervals for our study overlapped with the London study a crude adjustment of our prevalence figure, accounting for undiagnosed tremor dominant PD of leads to a corrected figure of 169 per 10^5 , very close to the results of Schrag and colleagues.

We are likely to have included cases in our prevalence figure who did not have PD. Only 35% of patients identified via database and record searching were examined face to face in the research clinic, and those cases had a 5% diagnosis revision rate. This would lead to a reduction in our total case figure of 12 cases (5% of 247 non-clinic cases) and a small reduction in the overall crude prevalence of 3% (12/380). The highest mis-diagnosis rates were in those patients followed up by non neurologists, although this analysis is based on a very small number of cases. The diagnostic accuracy of those patients who were solely followed up in primary care and did not attend the research clinic is unknown, and the

prevalence estimate may well have included cases of parkinsonism who did not fulfil Queen Square Brain Bank Criteria for PD. In addition, there may have been cases coded as PD who, despite the vigorous screening of primary care and secondary care records but did not attend the research clinic, and were included in the prevalence estimate but did not have PD.

The emphasis of this study was to obtain accurate onset data and estimate the prevalence of YOPD. Some of the constraints outlined above related to the need for a large denominator population to provide a reasonable estimate of the prevalence of young onset disease. As the majority of YOPD patients are referred to neurologists or a physician with an interest in movement disorders, the prevalence estimate, diagnosis and information on onset symptoms obtained is likely to be reasonably accurate.

4.4.2 Impact of Prevalence study on Furthering Knowledge of YOPD

This prevalence study is unique in that information on age at onset has been collected. We can therefore provide an estimate of YOPD prevalence. This information is essential in the planning of service provision for younger onset patients and may help also to define health care burden in this group of PD patients. This prevalent cohort provided the basis on which the community based case control study would be performed, studying the differences between YOPD and LOPD in a representative group of patients who were subject to less selection bias than many previous highly selected clinic based studies. Studying the clinical differences between YOPD and LOPD in this way may reveal some aetiological clues but will also identify specific management issues relating to differences in the social, financial and psychosocial demands between these groups. Also in the planning and executing of this study we have helped to raise the awareness of PD in the younger population both in the community and to health care workers, hopefully leading to earlier diagnosis and more appropriate referral to specialist services.

4.4.3 Conclusion

The UK healthcare system offers an opportunity to study the epidemiology of disease by offering access to health care free of charge to everyone. Future researchers should be aware of difficulties if solely relying on primary or secondary care electronic diagnostic

coding records and recognise that supplementation of detailed clinic letters and face to face examination of patients is essential to increase accuracy of estimates.

In conclusion, the prevalence estimate form this study provides further evidence on the geographical and temporal distribution of PD and suggests that rates have remained relatively constant over the last 40 years.

Although PD is seen as a disease of the elderly, YOPD is far more common than appreciated in the prevalent PD population and the provision of health and social care for these patients should be an important consideration.

Chapter 5 Non Motor Features of Young versus Late Onset Parkinson's Disease

5.1 Chapter Summary

We analysed PD patients from the prevalence study and a regional cohort. The presence of non motor features was examined and compared in groups separated by age at onset. We also compared prevalence and regional cohort patients to look for evidence of selection bias. Direct questions were used to gather information on the presence of prodromal features including constipation, loss of smell, sleep disorders, depression, pain and paraesthesiae. In addition, validated standardised scales were used to investigate cognition at time of assessment (MMSE), daytime sleepiness (Epworth Sleepiness Scale) and depression (Beck's Depression Inventory). Chi squared and t test analyses were used to compare proportions and mean scores across different onset groups. Significant differences were seen between YOPD and LOPD. Hyposmia, constipation and sleep disturbance was reported to occur more commonly by LOPD patients in the premotor phase. In established disease, depression, paraesthesiae and sleep disturbance was more common in YOPD and dementia was less common than in LOPD.

5.2 Introduction

PD is a motor disorder, with diagnostic criteria based on motor impairment and response to treatment (Litvan, Bhatia *et al.* 2003). In recent years it has become clear that some non-motor features are very common in patients with PD, and this has been related to the presence of Lewy body disease. Williams and colleagues identified hallucinations to be a very common feature in Parkinsonian disorders, particularly associated with Lewy body pathology (Williams, Warren *et al.* 2008). Other important non-motor features include REM (rapid eye movement) sleep behaviour disorder, constipation, depression, autonomic disturbance and sensory disturbance (Poewe 2008). Our concept of PD is in the process of changing from a motor disorder to one in which multiple brain systems are affected by Lewy body degeneration with a characteristic clinical and pathological pattern associated with Lewy body disease. Degeneration of the cholinergic basal forebrain structures may lead to depression and/or cognitive involvement, Lewy body degeneration of the olfactory bulbs causes hyposmia, involvement of the myenteric

plexus of the gut causes constipation, and involvement of the lower brainstem may relate to sleep disturbance (Braak, Del Tredici *et al.* 2003; Braak, Bohl *et al.* 2006; Poewe 2008). The Braak hypothesis suggest that non-motor non-dopaminergic brain areas (dorsal motor nucleus of the vagus, lower brainstem nuclei, olfactory bulb) are involved in the pre-nigral phase (stages 1 and 2). This corresponds to reports by some patients of prodromal constipation, hyposmia, REM sleep behavioural disorder and depression before the onset of motor symptoms of PD (Ansari and Johnson 1975; Doty, Stern *et al.* 1992; Schenck, Bundlie *et al.* 1996; Ashraf, Pfeiffer *et al.* 1997; Gonera, van't Hof *et al.* 1997; Olson, Boeve *et al.* 2000; Abbott, Petrovitch *et al.* 2001; Nilsson, Kessing *et al.* 2001; Nilsson, Kessing *et al.* 2002; Schuurman, van den Akker *et al.* 2002; Hawkes 2003; Leentjens, Van den Akker *et al.* 2003; Lauterbach, Freeman *et al.* 2004; Ponsen, Stoffers *et al.* 2004; Sommer, Hummel *et al.* 2004; Ueki and Otsuka 2004; Chaudhuri, Healy *et al.* 2006; Iranzo, Molinuevo *et al.* 2006; Ishihara and Brayne 2006; Kaye, Gage *et al.* 2006; Ross, Abbott *et al.* 2006; Ross, Petrovitch *et al.* 2008). It has been hypothesized that future disease modifying treatment will need to be given very early in the disease course and understanding this pattern of symptom progression is likely to become very important in the early symptomatic diagnosis of PD. It is possible that the pattern of prodromal and motor-associated non-motor symptoms will be valuable in the differentiation of clinical sub-types of PD. To date no published study has systematically compared the prevalence of non-motor symptoms in YOPD and LOPD. This chapter reports the findings of our study of non motor symptoms in YOPD and LOPD.

5.3 Results

5.3.1 Study Cohort

Our total sample size was 450 (358 clinic assessments, 92 questionnaire only). Almost all (98%) patients had a disease duration of one year or more at the time of assessment, but the mean interval from onset to diagnosis was 4 years, and from diagnosis to assessment was 7 years. Delay to diagnosis was significantly longer in those with onset under 45 (5.2 vs. 3.7 $p=0.009$) as was the interval from diagnosis to study assessment (10.4 vs. 6.4, $p<0.0001$). The patients were approximately evenly distributed in the four age bands with the youngest onset patients having the longest disease duration (Table 5-1).

Table 5-1 : Clinical Characteristics of Study cohort

	Total	*Onset <45*	*Onset 45-54*	*Onset 55-64*	*Onset ≥65*	*p- value*
n (M:F)	**450 (1: 0.6)**	96 (1: 0.7)	119 (1: 0.6)	114 (1: 0.7)	121 (1: 0.6)	0.98
Mean age at onset (range, yrs)	**56 (8-85)**	39(8-44.9)	51 (45-54.9)	60 (55-64.9)	72 (65-85)	< 0.0001
Mean current age (range, yrs)	**65 (28-90)**	52 (28-66)	60 (48-79)	67 (58-85)	78 (67-90)	<0.0001
Mean disease duration (range, yrs)	**9 (0.5-39)**	13 (1-39)	10 (1-28)	8 (1-24)	6 (0.5-22)	<0.0001
Mean Motor UPDRS score (range/ 108)	**29 (2-72)**	25 (4-57)	28 (3-72)	28 (2-62)	32 (12-71)	0.0016

Clinical Characteristics of Prevalent and Non Prevalent Cohorts

	Prevalent Cohort			
	Onset <45	***Onset 45-54***	***Onset 55-64***	***Onset ≥65***
n	10	14	42	87
Mean age at onset (range, yrs)	40.5 (29-44.9)	50.3 (45.7-54.1)	60.3 (55.1-64.9)	72.7 (65-85.3)
Mean current age (range, yrs)	51.4 (43-55.6)	61.8 (49.7-79.4)	67.6 (58.3 – 85.1)	78.9 (76-90.3)
Mean disease duration (range, yrs)	10.9 (2.7-25.8)	11.6 (2-27.1)	7.3 (1.2-23.7)	6.2 (0.4-21.7)
Mean Motor UPDRS score (range/ 108)	26.9 (14-57)	28.1 (15-42)	28 (2-62)	31.6 (12-71)

	Non Prevalent Cohort			
	Onset <45	***Onset 45-54***	***Onset 55-64***	***Onset ≥65***
n	86	105	72	34
Mean age at onset (range, yrs)	38 (8.1-44.9)	50.7 (45.1-54.9)	59.1(55.1-64.9)	70.1 (65.8-84.1)
Mean current age (range, yrs)	51.8 (27.8-66.4)	60.2 (47.5-77.5)	66.8 (57.8-82.1)	74.2 (68.2-87.3)
Mean disease duration (range, yrs)	13.5 (1.1-38.7)	9.5 (1.1-28.3)	7.8 (0.9-27.3)	4.1 (0.7-13.4)
Mean Motor UPDRS score (range/ 108)	24 (4-57)	28.2 (3-72)	28.2 (9-60)	33.1 (15-58)

5.3.2 Prodromal Non Motor Features

Constipation, depression, fatigue, sleep disturbance, hyposmia, parasthesiae and pain or cramps were common as prodromal features affecting between 13-31% of all PD patients (Table 5-2). The commonest reported prodromal NMS in our total study population was hyposmia (31%). A quarter of the patients reported fatigue as a feature occurring before the onset of motor symptoms, and sleep disturbance and constipation were reported in about 20%.

In YOPD, sleep disturbance was reported less frequently prior to the onset of motor symptoms than in LOPD. The negative association between prodromal hyposmia and YOPD was particularly striking with a significant increase in the frequency of prodromal hyposmia in PD patients with age at onset greater than 45. Similarly, constipation was reported as a prodromal symptom more frequently with advancing age (table 5-2).

Table 5-2 : Frequency of Prodromal NMS

		Onset group						
Symptom	*Total Group n (%)*	*<45 n (%)*	*45-54 n (%)*	*55-64 n (%)*	*≥65 n (%)*	*Heterogeneity (χ2 test, p)*	*Trend (χ2 test, p)*	*<45 vs ≥45 (χ2 test, p)*
Hyposmia	**109 (31)**	11(16)	39 (40)	28(32)	31(32)	0.017	0.20	0.004
Constipation	**71 (20)**	11 (16)	15 (15)	19(22)	26(27)	0.18	0.043	0.39
Cramps/pain	**82 (29)**	13 (26)	26 (35)	21(26)	22(27)	0.60	0.75	0.59
Fatigue	**86 (25)**	13 (19)	30 (30)	20(22)	23(24)	0.40	0.97	0.28
Sleep disturbance	**79 (23)**	9 (13)	28 (28)	21(24)	21(22)	0.16	0.51	0.048
Depression	**55 (16)**	13 (20)	16 (16)	14(16)	12(12)	0.68	0.24	0.35
Parasthesiae	**47 (13)**	8 (12)	18 (18)	11(13)	10(10)	0.41	0.38	0.73

5.3.3 Current Non Motor Features at time of assessment

Constipation, depression, fatigue, sleep disturbance, hyposmia, parasthesiae and pain or cramps were common features affecting between 19-70% of all PD patients at time of assessment.

A significantly higher proportion of YOPD patients reported depression, sleep disturbance and parasthesiae at time of assessment than LOPD, and there was a significant trend for decreasing frequency of these symptoms with increasing age at onset (Table 5-3).

Table 5-3 : Current NMS by age at onset

		Onset group						
Symptom	*Total Group n(%)*	*<45 n (%)*	*45-54 n (%)*	*55-64 n (%)*	*≥65 yrs n (%)*	*Heterogeneity (χ^2 test, p)*	*Trend (χ^2 test, p)*	*<45 vs >45 (χ^2 test, p)*
Fatigue	**186 (67)**	34(71)	46(73)	57(69)	49(60)	0.33	0.12	0.58
Sleep disturbance	**192 (70)**	40(82)	44(70)	63(76)	45(56)	**0.006**	**0.004**	**0.04**
Cramps/pain	**144 (53)**	25(52)	36(57)	43(52)	40(50)	0.86	0.62	0.92
Constipation	**127 (46)**	21(43)	29(46)	40(49)	36(43)	0.85	0.94	0.66
Hyposmia	**124 (45)**	18(37)	36(57)	38(46)	32(39)	0.097	0.60	0.21
Parasthesiae	**57 (21)**	16(33)	13(21)	16(20)	12(15)	0.11	**0.023**	**0.023**
Depression	**53 (19)**	15(30)	16(26)	14(17)	8(10)	**0.016**	**0.0015**	**0.032**
Dementia (MMSE <24)	**22 (6)**	2 (3)	6 (6)	3 (3)	11(11)	0.07	**0.043**	0.20
MMSE ≥ 27	**302 (84)**	63 (90)	92 (89)	75 (85)	72 (74)	**0.011**	**0.0022**	0.15
Depression (BDI≥10)	**218 (49)**	56 (60)	63(53)	46 (41)	53 (44)	**0.032**	**0.008**	**0.021**
Hallucinations	**67 (19)**	12(17)	26(25)	15(17)	14(14)	0.23	0.28	0.71
Epworth >10	**224 (55)**	43 (58)	66 (58)	55 (53)	60 (56)	0.64	0.62	0.28
Insomnia	**175 (49)**	38(54)	54(53)	47(53)	36(37)	0.055	**0.026**	0.33
RBD	**168 (47)**	33(47)	50(49)	49(56)	36(37)	0.087	0.26	0.97

5.3.4 Neuropsychiatric features

Hallucinations were reported by 19% of all PD patients but there was no significant difference between YOPD and LOPD groups (p=0.23) (Table 5-3).

Six percent of all patients had dementia as defined by a MMSE score of less than 24 (clinical dementia), and 84% had a score of 27 and above (clinically normal). Those with onset under 45 had significantly higher proportion of cases with clinically normal MMSE than those with onset above 65 years (90% vs. 74%, p=0.01), and there was a significant trend with increasing age at onset (p=0.002) (Table 5-3).

The frequency of YOPD with clinical dementia defined as MMSE < 24 was significantly different between YOPD and LOPD, 3% in onset <45 years compared with 6% in onset >45 years and 11% in onset over 65 years (Table 5-3).

Comparing the mean MMSE score in groups divided at onset below 45 years and at or above 45 years showed a small but significant difference (YOPD mean MMSE 28.7, LOPD mean MMSE 27.9, p=0.02) (Table 5-4).

Table 5-4 : Mean MMSE scores in onset groups split at onset before and at or above 45 years

	N	Mean MMSE (95% CI)	p value
Onset <45 years	69	28.7 (28.2-29.1)	0.02
onset ≥ 45 years	287	27.9 (27.6-28.2)	

However, these data may be confounded by differences in disease duration and current age. Having adjusted for disease duration, the association between age of onset and MMSE becomes stronger, with LOPD patients have lower MMSE scores (Table 5-5). Conversely, correcting for age at onset shows the correlation between longer disease duration and deterioration in MMSE (coefficient 0.19, p<0.001, 95%CI 0.12-0.28).

Therefore both older age at onset and longer disease duration are associated with deterioration in MMSE.

Table 5-5 : Multiple Regression Analysis showing effect of onset group on MMSE after adjusting for disease duration

	Onset <45 used as baseline group			Adjusted for disease duration		
	Coefficient	P value	95% CI	Coefficient	P value	95% CI
Onset 45-54	0.06	0.58	-0.15 to 0.27	0.16	0.14	-0.05 - 0.37
Onset 55-64	0.22	0.048	-0.002 to 0.44	0.37	**0.001**	0.15 – 0.59
Onset ≥ 65	0.41	<0.001	0.20 to 0.63	0.66	**<0.001**	0.44 – 0.89

When depression was assessed using the BDI 50% of all PD patients were depressed (BDI ≥ 10); 32% had mild depression, 8% moderate and 1% severe (Table 5-7).

When divided by onset at 45 years, YOPD patients have significantly higher mean BDI scores than LOPD (11.8 vs. 8.8, p=0.0003) (Table 5-6).

Table 5-6 : Mean BDI scores in onset groups split at onset before and at or above 45 years

	N	Mean BDI score (95% CI)	p value
onset <45 years	80	11.8 (9.9-13.6)	0.0003
onset ≥ 45 years	308	8.8 (8.1-9.4)	

The proportion of patients with depression as defined by a BDI score of over 10 was significantly higher in younger onset patients and decreased with increasing age at onset. (Table 5-3).

Table 5-7 : Depression by BDI Score

	Total Group N (%)	*Onset <45 yrs n (%)*	*Onset 45-54 yrs n (%)*	*Onset 55-64 yrs n (%)*	*Onset ≥65 yrs n (%)*	*Het X^2 p value*	*Onset <45 vs ≥45 , Het X^2 p value*
none/minimal (BDI < 10)	**227 (59)**	38 (48)	56 (53)	65 (68)	68 (64)	0.01	0.001
mild-moderate (BDI 10-18)	**127 (33)**	28 (35)	40 (38)	26 (27)	33 (31)		
moderate- severe (BDI 10-29)	**29 (8)**	10 (13)	8 (8)	5 (5)	6 (6)		
Severe (BDI ≥ 30)	**5 (1)**	4 (5)	1 (1)	0 (0)	0 (0)		

Longer disease duration was associated with higher BDI scores when controlled for age at onset (coefficient 0.11, p<0.05, 95% CI 0.002-0.22). However, adjusting for disease duration only slightly attenuated the difference with YOPD patients were still more likely to be depressed on the BDI than LOPD (Table 5-8).

Table 5-8 : Multiple regression analysis showing effect of onset group on BDI Score after adjusting for disease duration

	Onset <45 used as baseline group			**Adjusted for disease duration**		
	Coefficient	P value	95% CI	Coefficient	P value	95% CI
Onset 45-54	-0.29	0.04	-0.57 to 0.08	-0.24	0.10	-0.53 to 0.04
Onset 55-64	-0.52	<0.001	-0.81 to -0.24	-0.43	**0.005**	-0.73 to -0.13
Onset ≥ 65	-0.44	0.002	-0.72 to -0.16	-0.31	0.05	-0.62 to 0.004

5.3.5 Sleep Disturbance

Excessive daytime sleepiness was common overall in the whole group of PD patients affecting 55 % (ESS score ≥ 10) but there was no significant difference between YOPD and LOPD groups at time of assessment (Tables 5-9 and 5-10).

Table 5-9 : Mean Epworth Sleepiness Scales Scores in onset groups split at onset before and at or above 45 years

	N	mean (95% CI)	p value
onset <45 years	87	10.2 (8.9-11.6)	0.68
onset ≥ 45 years	324	10.5 (9.9-11.2)	

Table 5-10 : Sleepiness scores from Epworth Sleepiness Scale Scores

	Total Group n (%)	*onset <45 yrs n (%)*	*onset 45-54 yrs n (%)*	*onset 55-64 yrs n (%)*	*onset ≥65 yrs n (%)*	*Heterogeneity X^2 p value*	*Onset <45 vs ≥45 , X^2 p value*
not sleepy (ESS<10)	**187 (42)**	44 (47)	47 (40)	48 (43)	48 (40)	0.78	0.34
sleepy (ESS=10-17)	**166 (37)**	29 (31)	49 (41)	39 (35)	49 (41)		
very sleepy (ESS≥18)	**92 (21)**	21 (22)	23 (19)	22 (22)	24 (20)		

Table 5-11 : Multiple regression analysis showing effect of onset group on Epworth Score after adjusting for disease duration

	Onset <45 used as baseline group			**Adjusted for disease duration**		
	Coefficient	P value	95% CI	Coefficient	P value	95% CI
Onset 45-54	0.14	0.27	-0.11 to 0.40	0.25	0.06	-0.01 - 0.51
Onset 55-64	0.01	0.93	-0.25 to 0.27	0.18	0.21	-0.10 - 0.45
Onset ≥ 65	0.06	0.65	-0.20 to 0.32	0.31	0.04	0.02 - 0.60

Longer disease duration was significantly associated with higher Epworth scores when controlling for age at onset (coefficient 0.18, p<0.001, 95%CI 0.08-0.27). When disease duration was adjusted for, LOPD patients had significantly higher scores (more sleepy) than younger onset groups (Table 5-11).

Insomnia affected 49% of all PD patients. There was a significant trend for the younger onset groups to report more insomnia, but this lost statistical significance when the older onset groups were merged. REM sleep behavioural disorder was common (47%) overall but was not significantly different in YOPD and LOPD (Table 5-3).

5.3.6 Cardiff Community based vs Non Cardiff Supplementary secondary care referred cases

Cases from outside Cardiff were specifically recruited to increase the number of patients with YOPD. As these cases were ascertained from secondary care, this may have introduced an element of selection bias, so analysis was performed to investigate whether there were any significant differences between prevalent and non prevalent cases.

Cardiff cases were significantly older at time of assessment (72 vs. 60 years, p=0.0001), had older age at onset (65 vs. 51, p=0.001) and had a shorter disease duration (7 vs. 10 years, p=0.002) than non prevalent cases (Table 5-12).

Table 5-12 : Baseline Characteristics of Cardiff vs Non-Cardiff Cases

	Cardiff Cases	*Non-Cardiff Cases*	*P value*
n (M:F)	153 (1:0.6)	292 (1:0.6)	
Mean age at onset (range, yrs)	65 (29-85)	51 (8-84)	0.0001
Mean current age (range, yrs)	72 (43-90)	60 (28-87)	0.0001
Mean disease duration (range, yrs)	7 (0.5-27)	10 (0.7-39)	0.002

5.3.7 YOPD (onset <45) Cardiff vs Non-Cardiff cases

As YOPD cases were supplemented from secondary care sources in addition to the community based prevalent cohort, it was important to see if any differences existed between the YOPD patients ascertained from the Cardiff and non-Cardiff sources. Comparing the Cardiff and non-Cardiff cases in those with onset under 45 did not show any significant differences in the frequencies of non motor symptoms or in mean MMSE, Epworth or BDI scores (Table 5-13).

Table 5-13 : NMS in Cardiff and Non-Cardiff Cases with onset <45

		Cardiff Cases (total 10) N (%)*	*Non-Cardiff Cases (total 86) N (%*)*	*P value*
Prodromal	**Constipation**	2 (20)	9 (15)	0.66
	Depression	1 (10)	14 (22)	0.39
	Fatigue	2 (20)	15 (23)	0.81
	Sleep Disturbance	3 (30)	8 (13)	0.16
	Hyposmia	0	12 (19)	0.13
	Parasthesiae	0	13 (20)	0.14
	Pain/cramps	0	18 (35)	0.05
At time of assessment	**Constipation**	4 (57)	25 (48)	0.65
	Depression	2 (29)	19 (37)	0.65
	Fatigue	6 (86)	41 (75)	0.52
	Sleep Disturbance	6 (86)	51 (86)	0.96
	Hyposmia	2 (29)	24 (46)	0.38
	Parasthesiae	3 (43)	25 (45)	0.93
	Pain/cramps	5 (71)	36 (63)	0.67
	Hallucinations	2 (20)	20 (25)	0.71
	MMSE <24	0	2 (2)	0.62
	MMSE >27	10 (100)	77 (92)	0.34
	Epworth ≥10	3 (33)	40 (51)	0.31
	BDI ≥ 10	5 (50)	51 (61)	0.51
	Mean MMSE	28.2	28.6	0.8
	Mean Epworth	9	10.4	0.5
	Mean BDI	10.2	12.0	0.53

* note not all cases provided information on every feature thus percentages relate to variable total numbers

5.3.8 YOPD (onset <55) Cardiff vs. Non-Cardiff cases

Comparing the Cardiff and non-Cardiff cases in those with onset under 55 did not how any significant differences in the frequencies of non motor symptoms or in mean MMSE, Epworth or BDI scores (Table 5-15).

Table 5-14 : NMS in Cardiff vs. Non-Cardiff cases with onset <55

		Cardiff Cases (total 24) N (%)*	*Non-Cardiff Cases (total 191) N (%*)*	*P value*
Prodromal	**Constipation**	5 (24)	24 (15)	0.33
	Depression	4(18)	32 (20)	0.84
	Fatigue	10 (43)	42 (27)	0.09
	Sleep Disturbance	9 (41)	34 (22)	0.05
	Hyposmia	7 (32)	49 (31)	0.95
	Parasthesiae	4 (20)	30 (19)	0.90
	Pain/cramps	4 (20)	46 (37)	0.13
At time of assessment	**Constipation**	11 (58)	53 (48)	0.41
	Depression	7 (39)	37 (33)	0.65
	Fatigue	14 (74)	90 (76)	0.86
	Sleep Disturbance	16 (84)	96 (79)	0.58
	Hyposmia	10 (53)	62 (54)	0.89
	Parasthesiae	6 (35)	39 (34)	0.91
	Pain/cramps	12 (33)	77 (64)	0.93
	Hallucinations	8 (33)	45 (25)	0.37
	MMSE <24	0	8 (4)	0.30
	MMSE >27	23 (96)	172 (91)	0.42
	Epworth ≥10	12 (52)	97 (55)	0.81
	BDI ≥ 10	12 (50)	107 (57)	0.54
	Mean MMSE	28.7	28.5	0.7
	Mean Epworth	10.6	10.7	0.97
	Mean BDI	9.8	10.7	0.6

* note not all cases provided information on every feature thus percentages relate to variable total numbers

These data suggest that the use of non-Cardiff cases did not introduce significant bias in the assessment in the variation of non-motor symptoms.

5.4 Discussion

NMS have commonly been reported in studies of PD patients from specialty hospital based populations. With the exception of dementia and neuropsychiatric features (see Chapter 2) NMS have not been systematically studied in YOPD. We have explored the occurrence of NMS, both predating the motor symptoms of PD and at time of assessment in established disease, and the differences between YOPD and LOPD in a large community based study. NMS represent one domain in which there are significant phenotypic differences between YOPD and LOPD.

5.4.1 Prodromal non motor symptoms

In a retrospective case note study of pathologically proven PD, 21% of patients were found to have presented with NMS i.e. preceding the onset of motor symptoms of PD (O'Sullivan, Williams *et al.* 2008). In our study, about a third of patients with PD self reported the occurrence of NMS as predating their motor onset of PD, the commonest symptom being hyposmia. The preclinical phase of nigral degeneration in PD predicted from neuropathological studies and neuroimaging has been suggested to range between 5 and 7 years (Fearnley and Lees 1991; Morrish, Rakshi *et al.* 1998; Brooks 2000; Marek, Innis *et al.* 2001). Several non motor symptoms of PD have been reported to precede motor onset by many years suggesting the involvement of non dopaminergic systems. The retrospective nature of ascertaining the prevalence of prodromal non motor symptoms is a limitation in itself because of recall bias, and most studies, including our own, may not accurately determine the prevalence of NMS. There are some estimates of the background population rate of some of these symptoms. For example, the prevalence of constipation in the general population of Europe has been reported between 5-35% (Peppas, Alexiou *et al.* 2008). The association of prodromal non motor symptoms with PD can only be satisfactorily studied with a large prospective cohort study. Olfactory dysfunction has been reported by some investigators as a preclinical marker of PD (Ansari and Johnson 1975; Doty, Stern *et al.* 1992; Hawkes 2003; Ponsen, Stoffers *et al.* 2004; Ross, Abbott *et al.* 2006). One study reported hyposmia as a feature at PD motor onset in 68% of cases (Henderson, Lu *et al.* 2003). Amongst senior citizens who were

screened for olfactory dysfunction, those with the worse olfactory tests scores had a four times greater risk of developing PD (Ross, Petrovitch *et al.* 2008). In first degree relatives of PD patients, 10% of those with olfactory dysfunction developed PD within 2 years and so the authors suggested the presence of hyposmia in the at risk population could be used as a preclinical marker of PD (Ponsen, Stoffers *et al.* 2004). REM sleep behavioural disorder (RBD) has been reported to precede motor onset of PD in over 40% in some studies (Schenck, Bundlie *et al.* 1996; Chaudhuri, Healy *et al.* 2006). Excessive daytime sleepiness (EDS) has also been found to be a risk factor for developing PD (Abbott, Ross *et al.* 2005). Constipation has been shown to be associated with a threefold risk of developing PD over a ten year interval (Abbott, Petrovitch *et al.* 2001). Depression had also been shown to precede the onset of PD (Gonera, van't Hof *et al.* 1997; Nilsson, Kessing *et al.* 2001; Schuurman, van den Akker *et al.* 2002; Leentjens, Van den Akker *et al.* 2003; Lauterbach, Freeman *et al.* 2004; Ishihara and Brayne 2006). About 20% of PD patients report mood disturbance years before PD motor onset, especially during 3-6 years before diagnosis of PD (Mindham 1970; Robins 1976; Santamaria, Tolosa *et al.* 1986; Shiba, Bower *et al.* 2000; Leentjens, Van den Akker *et al.* 2003). Depression has been associated with a 2-3 fold increased risk of developing PD (Nilsson, Kessing *et al.* 2001; Leentjens, Van den Akker *et al.* 2003). Anxiety has been shown to precede the motor onset of PD (Shiba, Bower *et al.* 2000; Weisskopf, Chen *et al.* 2003). In one study 50% of PD patients reported anxiety, the mean onset of which was 1 year before PD motor onset (Henderson, Lu *et al.* 2003). Apathy and fatigue have also been suggested as pre motor manifestations of PD (Cooper, Sagar *et al.* 1991; Shiba, Bower *et al.* 2000; Chaudhuri, Healy *et al.* 2006).

In order to accurately evaluate prodromal symptoms a detailed large scale study of the general population or a smaller study of high risk individuals, for example those at risk of familial PD, would be needed. The frequency of NMS become much higher as the disease course extends, and the profile of prodromal NMS differs from that of NMS in established disease. Hyposmia and cramps or pain (recalled by approx 30%) are the commonest reported NMS predating the onset of motor symptoms whereas sleep disturbance and fatigue (both reported by 70%) are more common in established disease. This may reflect the progression of pathology with time (Braak stages) with increasingly frequent involvement of the lower brainstem nuclei. The preclinical diagnosis of PD may

be aided by the recognition of these prodromal features and become important when considering the impact of disease modifying treatments and neuroprotective agents.

Our study is the first to show that the profile of prodromal NMS differs between YOPD and LOPD. In our cohort, prodromal hyposmia, constipation and sleep disturbance are more common in late onset disease. This may be explained if these features are more common purely with advancing age and control group comparison would be needed to clarify this issue. It is possible that the observations seen in our cohort may reflect differences in regional pathological change early in the disease course based on age at onset. Recent studies suggest an increase risk of developing PD if a combination of hyposmia, RBD and constipation were present, but our data suggest this is more relevant to LOPD (Ahlskog 2007).

5.4.2 Non motor symptoms in established disease

The rates of many of the NMS in our PD patients as a whole were similar to those reported previously. Sleep disturbance was reported in 70% of our cohort at time of assessment, excessive daytime sleepiness in 55%, REM sleep behavioural disorder in 47% and insomnia in 49%. The overall prevalence of sleep disturbance in PD has previously been reported as 60-98% (Lees, Blackburn *et al.* 1988; Factor, McAlarney *et al.* 1990; Nausieda 1992; Schenck, Bundlie *et al.* 1996; Tandberg, Larsen *et al.* 1998; Olson, Boeve *et al.* 2000; Stocchi, Vacca *et al.* 2001; Oerlemans and de Weerd 2002). Excessive daytime somnolence has been reported in 50% of PD patients (Abbott, Ross *et al.* 2005).

Hyposmia was self reported by 45% of our cohort at interview. However there is likely to be a marked discrepancy between awareness of hyposmia and its presence since, hyposmia, when tested objectively with smell tests, has been reported in over 90% of PD patients (Ansari and Johnson 1975; Doty, Stern *et al.* 1992; Montgomery, Baker *et al.* 1999; Abele, Riet *et al.* 2003; Hawkes 2003; Ponsen, Stoffers *et al.* 2004; Ross, Petrovitch *et al.* 2008).

In our cohort, constipation was reported by 46% of PD patients. Constipation has been previously reported in 57% of PD patients (Kaye, Gage *et al.* 2006).

Only 6% of our cohort had clinical dementia. This reflects the fact that our initial exclusion criteria excluded patients with severe dementia or psychiatric disease, which has lead to an underestimate of the prevalence of dementia in PD. The incidence of dementia in PD has previously been reported as 15-40% (Pollock and Hornabrook 1966; Aarsland, Tandberg *et al.* 1996; Rippon and Marder 2005; Ziemssen and Reichmann 2007). In a community based study of PD, dementia was reported in 41%, and the risk of developing dementia by age 85 was as high as 65% (Apaydin, Ahlskog *et al.* 2002). In a prospective study of PD patients, 26% developed dementia after 9 years, 52% after 13 years and 78% after 17 years (Aarsland, Andersen *et al.* 2003). A further study suggested that patients with PD had a 2-6 fold increased risk of developing dementia as compared to age matched controls (Emre 2003). However, although our study identified higher rates of cognitive impairment in later onset disease, we identified a small number of patients (3%) with disease onset below 45 with dementia. This indicates that the risk of dementia in YOPD although small is not negligible (see Chapter 2).

When asked at interview whether they thought themselves depressed, only 19% of our cohort answered yes. However, when assessed using the BDI, 49% of our cohort has depression as defined as a BDI score of over 10. Previous studies report depression in 4-70% of PD patients (Habermann-Little 1991; Cummings 1992; Hantz, Caradoc-Davies *et al.* 1994; Kostic, Filipovic *et al.* 1994; Tandberg, Larsen *et al.* 1996; Aarsland, Larsen *et al.* 1999; Slaughter, Slaughter *et al.* 2001; Burn 2002; Remy, Doder *et al.* 2005) . Anxiety has been reported in at least 40% (Aarsland, Larsen *et al.* 1999; Walsh and Bennett 2001).

Comparing the frequency of NMS in YOPD and LOPD, depression, sleep disturbance and parasthesiae were reported more often by YOPD patients at time of assessment. This is different to the profile of self reported prodromal NMS seen in YOPD and LOPD which may suggest different rates of progression of regional pathology.

Significant differences between YOPD and LOPD were found when using validated rating scales to evaluate clinical dementia and depression. Clinical dementia was more common in LOPD and depression was more common in YOPD even when adjustments were made for disease duration. These differences may relate to age or disease heterogeneity. Socio economic factors may play an important role in adding to depression in the YOPD group who are more likely to have a greater financial and social responsibility to their younger families.

5.4.3 Limitations

This study was primarily designed to be conducted on a community based cohort of patients ascertained for the prevalence study. However, only about a third of cases were obtained via this source and so not all cases were strictly community based in the comparison study of clinical features. Because the numbers of YOPD cases were small, this had to be supplemented by referral from secondary care sources from South Wales. This had the potential to introduce selection bias when integrating the secondary care cases, but we feel that this study is more representative study than the majority of previously published studies on YOPD based on very specialist clinic series. Analysis of the prevalent and non prevalent cases in the YOPD group showed no significant differences.

As this study examines established prevalent cases, one limitation of this study is the retrospective nature of estimating frequency of prodromal features. This relies on patient recall and awareness of symptoms and there may be differences according to age at onset and disease duration. This introduces an element of recall bias which may differ in the YOPD and LOPD groups. The younger onset cases had significantly longer disease duration and so may differentially influence how accurately details about symptom onset are remembered. Reporting bias may also occur, where YOPD cases may be more aware of symptoms and therefore report them more frequently, where older patients may ignore them by being put down to part of the ageing process. One possible way of overcoming this problem could be to follow up prospectively pre-symptomatic mutation carriers e.g. LRRK2 G2019S, to record the exact age at which prodromal symptoms are first recognised.

There are obvious dangers in regrouping the data by age at onset bands as the differences seen may be artificially produced, for example where there is no overall heterogeneity seen between age bands but where regrouping onset over 45 years a significant difference is seen. This can be illustrated by the presence of prodromal sleep disturbance. Here there is no overall heterogeneity across the 4 age groups, but the youngest onset group reports significantly less prodromal sleep disturbance, and this is borne out by the heterogeneity test when comparing onset under 45 with all onset over 45. There is a danger in artificially inducing significance by arbitrarily using 45 as a cut off, but this was a cut off decided prior to collecting the data. In any case, the data do suggest a threshold effect with significant differences seen in the younger onset group. This is in keeping with the theory that the younger onset group may have a different disease process. A second data set o rmeta-analysis would be needed to confirm these observations were not seen by chance.

We aimed to give an overview of the prevalence of a broad range of non motor symptoms, and so the detail and depth in which each symptom could be examined was limited due to available time and resources. Each clinical assessment took on average two hours to complete and the majority of patients felt fatigued by the end of the session, so lengthening the assessment was not feasible. In addition, it would not have been possible to collect data on as many individual subjects given the constraints of the project timeline. There are many areas where more detailed assessments would have been beneficial. For example, instead of relying on patients recall regarding hyposmia, which has likely led to an underestimate of true prevalence, a more objective assessment using standard smell tests could have been used. This underestimation however applies to both YOPD and LOPD although it is unclear as to whether this occurs at a differential rate. Unfortunately, using severe dementia as an exclusion criteria at the GP ascertainment stage has led to a gross underestimation of dementia prevalence in our PD cohort. It is likely that a larger proportion of LOPD cases were excluded at the ascertainment stage, either due to physical or cognitive/neuropsychiatric morbidity. In addition, the cognitive assessment could have been improved by using the slightly longer but more sensitive cognitive screening tool the ACE-R (Addenbrooke's Cognitive examination revised version). In those patients where additional cognitive assessments were required, there

are vast arrays of tests available but require a great deal of time to perform and require the patient to be rested and comfortable for results to be reliable. During the course of this study the NMS-Quest was published (Chaudhuri, Martinez-Martin *et al.* 2006). This is a standardised validated self completion questionnaire designed to address the presence of non motor symptoms in PD. However, this questionnaire was created to aid the physician identify clinical problems relating to non motor symptoms, not as a research tool to investigate frequencies of non motor symptoms in PD. There are many questionnaires available to screen for depression and sleep disturbance. In this study we chose the most widely used scales in PD research, the Beck's Depression Inventory and the Epworth Sleepiness Scale. Both these scales are general self completion questionnaires, not specific for PD but have been validated in assessment for PD patients. Subsequently, PD specific scales have been published, for example the Sleep-PD questionnaire which tailors questions to PD sufferers.

It is likely there is a relationship between sleep disturbance, depression and cognitive dysfunction, all three commonly coexisting in PD. The effects of this interaction were not investigated in this thesis.

5.4.4 Strengths

Our study is based on a large community based sample of PD patients, although supplemented by secondary care resources in South Wales, we still believe this to be more representative than the highly selected hospital clinic based studies that make up most of the published data to date.

Data have been obtained on the frequencies of a broad range of non motor symptoms in PD. The aim was to describe a phenotypic profile for YOPD and LOPD by identifying the presence of as many non motor symptoms as possible rather than concentrating on a few symptoms in detail.

5.4.5 Pathophysiology

The Braak staging hypothesis offers some insights into non-motor symptoms in PD. This hypothesis suggests PD pathology begins in the lower brainstem (medulla) then ascends

to involve the midbrain, forebrain then the limbic cortex and neocortex. The nigro-striatal dopaminergic systems only become involved in the intermediate stages (stages 3 and 4).

Stages 1 and 2 are the pre-nigral stages involving non dopaminergic systems. Stage 1 includes involvement of the dorsal motor nucleus of the vagus nerve in the lower medulla, the small GABAergic nuclei of the pons and the anterior olfactory structures. Degeneration of these areas relate to constipation, REM sleep behavioural disorder and hyposmia respectively. In stage 2 the pathological process extends to areas mediating sleep homeostasis and mood disturbance such as thalamo-cortical pathway, pedunculopontine nucleus, locus coeruleus, subcoeruleus and the raphe nuclei. In stage 3 the noradrenergic and cholinergic systems become involved and may be implicated in the pathophysiology of cognitive and neuropsychiatric features. The pars compacta of the substantia nigra first become involved in stage 3, when motor symptoms begin. This provides an explanation as to why some NMS, the clinical manifestation of non dopaminergic involvement, may precede motor symptoms of PD. Cortical structures then become involved. In the final two stages, severe damage to the autonomic, limbic and somatomotor systems can be compounded by functional deficits in neocortical association areas (Braak, Del Tredici et al. 2003), possibly explaining why the frequency of some NMS increases with disease progression, such as cognitive, sleep and neuropsychiatric involvement . There have not been any detailed pathological studies looking at the staging processes or neuropathology as a whole in YOPD compared to LOPD but our results suggest that there may be significant differences in PD patients according to age at onset.

5.4.6 Further work

There is scope for more detailed evaluation of NMS in PD particularly in certain areas. Detailed smell testing can be performed not only to characterise the nature of smell deficit but also to identify hyposmia which may be asymptomatic.

The prevalence of dementia in the community based cohort can be estimated by ascertaining patients with severe cognitive dysfunction. It may be difficult to establish

new PD cases with established dementia and this may be best achieved with a longitudinal cohort study.

There are a variety of cognitive tests available which can help to define the exact domains involved in cognitive decline in some detail. Suggestions that subtle cognitive involvement in YOPD as compared with the normal population present another avenue of investigation (Hietanen and Teravainen 1988; Dubois, Pillon *et al.* 1990). Cognitive assessments in an incident cohort of PD patients only involved one patient with onset below 40 (Foltynie, Brayne *et al.* 2004) and so there exists a need for detailed cognitive assessments in large community based samples patients of YOPD.

Further non motor features on which frequencies were not reported on in this thesis include urinary dysfunction, sexual dysfunction, thermoregulatory dysfunction, orthostatic hypotension, cardiovascular involvement, psychosis, anxiety, apathy, panic attacks, impulse control disorders, obsessive compulsive disorder, dopamine dysregulation disorder and sleep apnoea.

The prospective follow up of presymptomatic mutation carriers may increase our accuracy in estimating frequency of prodromal NMS in the premotor phase of PD. Patterns of NMS manifestations studied in more detail may correlate to certain genetic aetiologies of PD and this may only become apparent as our understanding of PD risk factors increases.

5.5 Conclusions

Significant differences are seen in the profile of non motor symptoms of YOPD and LOPD, both prior to the development of cardinal motor features of PD and during the course of the disease. These data suggest that the pattern of prodromal and motor-associated non-motor symptoms will be valuable in the differentiation of clinical sub-types of PD separated by age at onset. This provides the basis on which investigating specific clinico-genetic correlations can be performed.

Chapter 6 Motor Features of Young versus Later Onset Parkinson's Disease

6.1 Chapter Summary

PD onset is defined by symptoms of motor involvement, namely tremor, rigidity, bradykinesia and postural imbalance. This chapter reports data on the clinical motor features of YOPD and LOPD in the community based prevalent cohort with supplementary cases from secondary care. Direct patient interview and correlation with medical case records were used to obtain information on onset symptoms, dystonia and dyskinesia. All cases were examined face to face in the research clinic in a practically defined "on" state. Standardised neurological examination, including the motor part of the UPDRS, was performed. Particular features of interest were presentation symptom, symmetry of signs and frequency of dystonia and treatment related dyskinesia. The relationship between dyskinesias and disease duration, age at onset, L DOPA dose and treatment duration was studies. The impact on quality of life was assessed using the Lang and Fahn activities of daily living (ADL) questionnaire. Significant differences are reported in the clinical motor features of YOPD and LOPD. YOPD patients presented more frequently with symptoms relating to akinesia and rigidity whereas LOPD more commonly presented with tremor. YOPD patients had more frequent dystonia and treatment related dyskinesias. Exercise induced dystonia is a specific characteristic of YOPD.

6.2 Introduction

PD is likely to be a heterogeneous disorder. It is likely that some patients with YOPD have a non-Lewy body disorder with distinct pathological and imaging characteristics. Parkin disease, which accounts for up to 20% of YOPD, has been associated with more severe and widespread dopaminergic depletion than typical LOPD and most cases do not have Lewy Bodies at post mortem (Mori, Kondo *et al.* 1998; Hayashi, Wakabayashi *et al.* 2000; van de Warrenburg, Lammens *et al.* 2001; Sasaki, Shirata *et al.* 2004). A few studies have described differences between the clinical motor features of YOPD and LOPD. The majority of these studies are based on hospital based study populations using a small number of cases. These previous observations may not reflect the true spectrum

of YOPD, as unusual cases may be overrepresented in these clinical settings. To try and address these issues, we have undertaken a community based study comparing clinical features of YOPD and LOPD.

6.3 Results

6.3.1 Study Cohort

Three hundred and fifty eight patients attended for clinical assessment. The mean age at assessment of the whole study population was 65 years (range 28-88), mean age at onset 56 years (8-84), mean disease duration was 9 years (1-39) and mean motor UPDRS 28/108 (2-72). There was no significant difference in these parameters between men and women.

Table 6-1 : Baseline characteristics of study population

	Total	*Onset <45 years*	*Onset 45-54 years*	*Onset 55-64 years*	*Onset ≥65 years*
N (M:F)	**358 (1:0.6)**	70 (1:0.7)	103 (1:0.6)	88 (1:0.6)	97 (1:0.6)
Mean age at onset (range)	**56(8-84)**	38 (8-44.9)	51 (45-55.9)	59 (55-64.9)	72 (65-85)
Mean current age (range)	**65 (28-88)**	51 (28-64)	61 (47-79)	67 (58-82)	77 (67-88)
Mean disease duration (range)	**9 (1-39)**	13 (1-39)	10 (1-28)	8 (1-24)	6 (1-27)
Mean motor UPDRS score	**28 (2-72)**	24 (4-57)	28 (3-72)	28 (2-62)	32 (12-71)

6.3.2 Onset Symptom

LOPD usually presents with tremor and YOPD usually presents with an akinetic rigid syndrome. Tremor is twice as common as a presenting symptom in patients with LOPD as compared to YOPD (onset over 65 vs. under 45), and akinetic rigid presentation is twice as common in YOPD as compared to LOPD (Tables 6-2 and 6-3).

Table 6-2 : Frequency of onset symptom by age at onset

	Whole group n (%)	*Onset <45 yrs n (%)*	*Onset 45-54 yrs n (%)*	*Onset 55-64 yrs n (%)*	*Onset ≥ 65 yrs n (%)*	*P value for het*	*P value for trend*	*P value for ≥ 45 yrs*
Tremor	**175 (49)**	21 (31)	41 (40)	53 (61)	66 (62)	0.001	0.0001	0.001
Slowness	**21 (6)**	6 (9)	6 (6)	3 (3)	6 (6)	0.57	0.45	0.26
Stiffness	**64 (18)**	24 (35)	19 (18)	10 (11)	11 (11)	0.001	0.0001	0.001
Balance	**2 (1)**	0	0	1 (1)	1 (1)	0.6	0.23	0.5
Walking	**22 (6)**	1 (1)	4 (4)	7 (8)	10 (10)	0.08	0.07	0.009
Frozen shoulder	**25 (7)**	8 (12)	10 (10)	7 (8)	0	0.012	0.0022	0.09
Handwriting	**22 (6)**	5 (7)	10 (10)	2 (2)	5 (5)	0.19	0.21	0.6
Reduced manual dexterity	**24 (7)**	3 (4)	13 (13)	4 (5)	4 (4)	0.048	0.29	0.39

When grouping akinetic rigid symptoms together, there were significant differences between onset groups. YOPD presented more commonly with akinetic rigid symptoms whereas tremor was the more common presentation for LOPD (Table 6-3).

Table 6-3 : Frequency of Tremor vs akinetic rigid onset by age of onset

	Whole group n (%)	*Onset <45 yrs n (%)*	*Onset 45-54 yrs n (%)*	*Onset 55-64 yrs n (%)*	*Onset ≥ 65 yrs n (%)*	*P value for het*	*P value for trend*	*P value for ≥ 45 yrs*
Tremor onset	**175 (49)**	21 (31)	41 (40)	53 (61)	66 (62)	0.001	0.0001	0.001
Akinetic Rigid onset	**156 (44)**	46 (68)	58 (56)	26 (30)	26 (27)	0.001	0.0001	0.001
Balance/ walking	**24 (7)**	1 (1)	4 (4)	8 (9)	11 (11)	0.04	0.05	0.004

6.3.3 Asymmetry of Parkinsonian signs

Asymmetry scores were calculated using the UPDRS motor score at assessment and comparing right and left sided scores for tremor, bradykinesia and rigidity in the limbs. If the ratio of the most affected side to the least affected side was over 1.5 this was classed as asymmetric. Based on the UPDRS motor examination, there was no evidence that disease asymmetry differed with age at onset. This was the case even after adjustment for disease duration (Table 6-4).

Table 6-4 : Asymmetry at assessment by age at onset stratified by disease duration

Disease duration (yrs)	Onset <45 years	Onset ≥45 years	Total	P value
< 5	80%	78%	79%	0.9
5-10	82%	70%	72%	0.3
≥10	59%	49%	52%	0.3

6.3.4 Dystonia

Dystonia of any kind was reported by 35.5% of the total cohort. Twenty seven percent reported dystonia before commencement of L dopa therapy, and 33.5% during treatment. In YOPD, dystonia occurring prior to treatment with L-dopa was significantly more common than in LOPD (at onset, within the first two years and exercise induced dystonia). During treatment with L-dopa, off period (including early morning) and peak dose dystonia were also significantly more common in YOPD. There was a significant trend for these types of dystonia to become less common with increasing age at onset (Table 6-5). The threshold for dystonia at onset and during the first two years of treatment (early dystonia) seemed to occur at an age at onset of 55 – dystonia at onset affected 20% of those whose disease started before the age of 55, and 4.3% of those whose disease started over the age of 54.

Table 6-5 : Frequency of Dystonia by age at onset

	Whole group n (%)	*Onset <45 yrs n (%)*	*Onset 45-54 yrs n (%)*	*Onset 55-64 yrs n (%)*	*Onset ≥ 65 yrs n (%)*	*P value for het*	*P value for trend*	*P value for ≥ 45 yrs*
Dystonia at onset	**41 (12)**	14 (20)	20 (20)	5 (6)	3 (3)	**0.001**	**0.0001**	**0.012**
Dystonia within 2 yrs	**21 (6)**	8 (11)	9 (10)	4 (5)	1 (1)	**0.014**	**0.0012**	0.03
Exercise induced dystonia	**33 (9)**	13 (18)	15 (15)	5 (6)	1 (1)	**0.001**	**0.0001**	**0.003**
Early morning dystonia prior to treatment	**2 (1)**	1 (2)	0	0	1 (1)	0.47	0.88	0.26
Off period dystonia	**44 (13)**	19 (30)	21(20)	4 (5)	0	**0.001**	**0.0001**	**0.001**
Peak dose dystonia	**15 (4)**	7 (11)	4 (4)	2 (2)	2 (2)	**0.031**	**0.01**	**0.004**
Early morning dystonia during treatment	**26 (8)**	14 (21)	7 (7)	4 (5)	2 (2)	**0.001**	**0.0001**	**0.001**
Dystonia not dose related	**34 (12)**	4 (9)	19 (15)	14 (17)	6 (7)	0.22	0.65	0.41

Exercise induced dystonia is a specific feature of YOPD occurring in a fifth of patients with onset below 45.

6.3.5 Dyskinesia

Eighty patients (23%) in our total cohort reported the presence of dyskinesia at the time of assessment. We obtained data on the frequency of dyskinesias and the impact on quality of life. When asked to clarify what proportion of the waking day dyskinesias were present 45 patients (13%) stated that dyskinesias were present for less than a quarter of their day, 24 patients (7%) between 26-50%, 5 patients (1%) between 51-75% and 6 patients (2%) reported dyskinesias to be present between 76-100% of their waking day. YOPD patients had reported significantly higher rates of dyskinesia than LOPD. There was a significant trend for this to diminish with advancing age at onset (Table 6-6).

Table 6-6 : Proportion of waking day reported to be affected by dyskinesia

	Whole group n (%)	***Onset <45 yrs n (%)***	***Onset 45-54 yrs n (%)***	***Onset 55-64 yrs n (%)***	***Onset ≥ 65 yrs n (%)***	***P value for het***	***P value for trend***	***P value for ≥ 45 yrs***
Dyskinesia present	80 (23)	28 (42)	32 (31)	13 (15)	7 (7)	**0.001**	**0.0001**	**0.001**
Dyskinesia present between 1-25% of waking day	45 (13)	10 (15)	20 (19)	9 (10)	6 (6)			
Dyskinesia present between 26-50% of waking day	24 (7)	14 (21)	6 (6)	3 (4)	1 (1)			
Dyskinesia present between 51-75% of waking day	5 (1)	3 (5)	2 (2)	0	0	**0.001**		
Dyskinesia present between 76-100% of waking day	6 (2)	1 (2)	4 (4)	1 (1)	0			
Average number of waking hours in dyskinetic state	4.7	5.5	4.9	4.0	2.7			

There was also a significant difference in the proportion of the waking day spent in a dyskinetic state between the onset groups (p=0.001), with the average number of hours spent in this state diminishing with as age at onset increased (Table 6-6).

Of those patients having reported dyskinesias (n=80), the mean Lang and Fahn ADL Dyskinesia quality of life scale score was 9/20 (s.d. 5.4). This significantly differed between onset groups, with YOPD having higher scores therefore reporting more disruption to their everyday quality of life then LOPD (4.2 vs. 1.7, p=0.001).

Relation to disease duration

In the whole group of patients regardless of whether dyskinesia was present or not, the YOPD patients had significantly longer disease duration. In the subset of patients who had dyskinesias, YOPD patients had a significantly longer disease duration than LOPD using both 45 and 55 as age definitions (15.6 vs. 12.2, p=0.02 and 14.4 s 10.4, p=0.01). This raised the possibility that the observed differences in dyskinesias were confounded by other factors. Further analysis was carried out.

Relation to L DOPA treatment duration and dose

In the subset of patients in whom dyskinesias were present and on whom data on L DOPA use were available, the dose of L DOPA was significantly higher and the duration of L DOPA treatment was significantly longer in the YOPD group using both 45 and 55 as age definitions.

Table 6-7 : Mean L DOPA treatment duration and dose in YOPD and LOPD in those with dyskinesia

	YOPD onset <45	*LOPD onset ≥ 45*	*P value*
Mean duration of L DOPA treatment (years)	7.2	4.5	0.002
Mean total L DOPA dose when seen in clinic (mgs)	470	418	0.004

	YOPD onset <55	*LOPD onset ≥ 55*	*P value*
Mean duration of L DOPA treatment (years)	5.9	4.1	0.004
Mean total L DOPA dose when seen in clinic (mgs)	472	388	0.004

Logistic regression examining factors associated with an increased risk of developing dyskinesia

Using logistic regression to look at the individual effects of age at onset, disease duration, duration of treatment with L DOPA and total L DOPA dose at time of clinic, all four factors were independently associated with an increased risk of developing dyskinesias. The effect of age at onset was seen more clearly in the onset division at 55 than 45 and this may be related to the smaller numbers in the under 45 age group. There is an apparent effect of dyskinesias becoming less common in the fourth quartile of disease duration in the multivariate analysis but the confidence intervals are wide.

Table 6-8 : Risk factors for developing dyskinesias

		Univariable				Multivariable		
		Odds ratio	95% CI	p-value		Odds ratio	95% CI	p-value
age at onset <45		2.9	1.6, 5.1	<0.0001		2.1	1.0, 4.8	0.07
Male		0.7	0.4, 1.1	0.13		0.6	0.3, 1.2	0.18
disease duration quartile	median (yrs)							
1	2.4	1.0				1.0		
2	5.7	1.4	0.3, 6.3	0.69		0.8	0.1, 4.6	0.76
3	9.4	19.3	5.7, 65.9	<0.0001		6.7	1.3, 33.8	0.02
4	16.3	22.6	6.6, 77.0	<0.0001		3.9	0.7, 21.2	0.12
p-value for trend				<0.0001				0.004
levodopa duration quartile	median (yrs)							
1	0.5	1.0				1.0		
2	1.8	0.9	0.3, 2.5	0.82		0.9	0.3, 2.9	0.81
3	4.5	3.3	1.4, 7.9	0.008		1.8	0.6, 4.9	0.27
4	11.9	6.3	2.7, 14.9	<0.0001		2.8	1.0, 7.8	0.05
p-value for trend				<0.0001				0.03
dose of levodopa quartile	mean/ median(mg)							
1	49/ 0 *	1.0				1.0		
2	282/ 300	1.9	0.8, 4.7	0.15		1.8	0.5, 7.3	0.38
3	430/ 400	4.1	1.8,9.1	0.001		2.2	0.6, 8.0	0.22
4	746/ 700	9.8	4.4, 21.8	<0.0001		5.4	1.5, 19.7	0.01
p-value for trend				<0.0001				0.001
age at onset <55		3.9	2.3, 6.8	<0.0001		3.8	1.8, 8.0	0.001
Male						0.6	0.3, 1.2	0.14
disease duration (quartiles)								
1						1.0		
2						0.6	0.1, 3.5	0.54
3						4.9	1.0, 25.2	0.06
4						0.6	0.3, 11.6	0.5
p-value for trend								0.04
levodopa duration (quartiles)								
1						1.0		
2						0.8	0.2, 2.6	0.7
3						1.8	0.6, 5.3	0.26
4						3.6	1.2, 10.4	0.02
p-value for trend								0.01
dose of levodopa (quartiles)								
1						1.0		
2						1.8	0.4, 7.4	0.41
3						2.0	0.5, 7.6	0.29
4						4.9	1.3, 18.3	0.02
p-value for trend								0.003

* first quartile includes cases who were not on L DOPA

6.3.6 Cardiff Community based vs Non Cardiff Supplementary secondary care referred cases

In our power calculations we anticipated recruiting 343 PD patients in Cardiff in whom 52 would have an age at onset <55 based on a 60% recruitment rate. In fact only 126 Cardiff cases were assessed in clinic of whom 20 had age at onset of under 55. Our recruitment from prevalence practices was 126/380 (33%) necessitating the need to identify more cases from outside Cardiff. All the cases from which these clinical features were collected attended a clinical assessment. Only one third of cases who attended for clinical assessment were recruited from the community based prevalence study and two thirds were ascertained from secondary care sources. This may have introduced an element of selection bias, so analysis was performed to investigate whether there were any significant differences between the Cardiff community based sample and the non Cardiff supplementary secondary care referred cases.

The community based cases were significantly older at time of assessment (72 vs. 61 years, p=0.0001), had older age at onset (65 vs. 51, p=0.001) and had a shorter disease duration (7 vs. 10 years, p=0.003) than non-Cardiff cases (Table 6-9).

Table 6-9 : Baseline characteristics of Cardiff vs. Non-Cardiff cases

	Cardiff Cases	*Non Cardiff Cases*	*P value*
n (M:F)	126 (1:0.7)	233 (1:0.6)	
Mean age at onset in yrs (range)	65 (29-85)	51 (8-84)	0.0001
Mean current age in yrs (range)	72 (43-88)	61 (28-87)	0.0001
Mean disease duration in yrs (range)	7 (1-27)	10 (1-39)	0.0003

6.3.7 YOPD (onset <45) Cardiff vs Non-Cardiff cases

Comparing the Cardiff and non-Cardiff cases in those with onset under 45 did not how any significant differences in the frequencies of motor symptoms or in mean Lang and

Fahn or UPDRS motor scores, except for peak dose dystonia which was more common in the Cardiff cases, although this was not corrected for multiple testing (Table 6-10).

Table 6-10 : Motor features in Cardiff vs non Cardiff cases with onset <45

	Cardiff Cases	*Non Cardiff Cases*	*P value*
Onset symptom			
- tremor	5 (50)	16 (27)	0.14
- slowness	0	6 (10)	0.30
- stiffness	2 (20)	22 (37)	0.30
- balance difficulties	0	0	-
- walking difficulties	0	2 (3)	0.56
- frozen shoulder	1 (10)	7 (12)	0.88
- handwriting difficulty	2 (20)	3 (5)	0.09
- difficulty turning in bed	0	0	-
- reduced manual dexterity	0	4 (7)	0.40
Akinetic rigid onset	5 (50)	42 (70)	0.21
Walking/balance onset	0	2 (3)	0.56
Dystonia at onset	4 (40)	10 (17)	0.10
Dystonia within 2 years of onset	1 (11)	7 (13)	0.88
Exercise induced dystonia	3 (30)	10 (17)	0.34
Early morning dystonia pre L dopa	0	1 (2)	0.69
Off period dystonia	5 (56)	14 (25)	0.06
Peak dose dystonia	3 (33)	4 (7)	**0.02**
Early morning dystonia on L dopa	4 (44)	10 (18)	0.08
Dystonia not related to L dopa dose time	0	4 (10)	0.39
Sleep benefit	12 (7)	2 (8)	0.29
Symmetry	6 (67)	35 (64)	0.86
Dyskinesia present	5 (50)	24 (41)	0.58
Mean L+F score whole group (95%CI)	5.9 (1-11)	3.9 (2-5)	0.35
Mean L+F score in those with dyskinesia (95% CI)	11.8 (6-17)	9.7 (7-12)	0.47
Mean UPDRS score (95% CI)	26.9 (18-36)	24 (21-27)	0.43

L+F = Lang and Fahn Dyskinesia ADL score

6.3.8 YOPD (onset <55) Cardiff vs Non-Cardiff cases

Comparing the Cardiff and non-Cardiff cases in those with onset under 55 did not how any significant differences in the frequencies of motor symptoms or in mean Lang and Fahn or UPDRS motor scores (Table 6-11).

Table 6-11 : Motor features in Cardiff vs non Cardiff cases with onset <55

	Cardiff Cases	*Non Cardiff Cases*	*P value*
Onset symptom			
- tremor	9 (45)	53 (35)	0.36
- slowness	0	12 (8)	0.19
- stiffness	5 (25)	38 (25)	0.99
- balance difficulties	0	0	-
- walking difficulties	0	6 (4)	0.38
- frozen shoulder	3 (15)	15 (10)	0.47
- handwriting difficulty	3 (15)	12 (8)	0.29
- difficulty turning in bed	0	0	-
- reduced manual dexterity	0	17 (11)	0.12
Akinetic rigid onset	11 (55)	94 (61)	0.58
Walking/balance onset	0	6 (4)	0.37
Dystonia at onset	7 (35)	27 (18)	0.07
Dystonia within 2 years of onset	1 (6)	16 (12)	0.48
Exercise induced dystonia	3 (15)	25 (17)	0.86
Early morning dystonia pre L dopa	0	1 (1)	0.72
Off period dystonia	6 (32)	34 (23)	0.39
Peak dose dystonia	3 (16)	8 (5)	0.09
Early morning dystonia on L dopa	4 (21)	17 (12)	0.25
Dystonia not related to L dopa dose time	1 (6)	13 (13)	0.44
Sleep benefit	2 (10)	12 (8)	0.75
Symmetry	14 (74)	86 (60)	0.25
Dyskinesia present	6 (30)	55 (36)	0.59
Mean L+F score whole group (95% CI)	4 (1-7)	4 (3-5)	0.91
Mean L+F score in those with dyskinesia (95% CI)	13 (8-17)	10 (8-11)	0.21
Mean UPDRS score (95% CI)	28 (23-32)	27 (25-29)	0.77

L+F = Lang and Fahn Dyskinesia ADL score

6.4 Discussion

6.4.1 Clinical features

Significant differences in the clinical motor features of YOPD and LOPD were seen. Age at onset seems to affect PD presentation. In this study cohort YOPD was much more likely to present with symptoms related to bradykinesia and rigidity whereas tremor onset was more common with increasing onset age. Previously published data have shown conflicting results regarding tremor presentation in YOPD. However, the majority are in agreement with our work and suggest tremor onset to be commoner in LOPD (Gibb and Lees 1988; Friedman 1994; Hely, Morris *et al.* 1995). However, Quinn *et al* showed tremor to be present in 52% of YOPD at presentation, and Giovaninni found tremor to be commoner in YOPD at presentation (Quinn, Critchley *et al.* 1987; Giovannini, Piccolo *et al.* 1991). However, our study is unique in that it is the only one to describe data from a community based cohort. Previously published data may be subject to selection bias as these studies are based on selected hospital based populations and may not be representative of the true YOPD population. Our data showed an agreement with the majority of previous studies – tremor was less common in YOPD. This was seen in both the community based cohort and non Cardiff supplementary cases, though only about forty percent of the cases identified as prevalent consented to participate in the clinical features study potentially introducing a degree of selection bias. However, we believe our study to be more representative than the majority of studies on which previous reported literature is based. The pathophysiological basis of Parkinsonian tremor is unknown but functional imaging and pharmacological studies suggest that Parkinsonian tremor may have a different pathological basis to Parkinsonian bradykinesia or rigidity (Fishman 2008). Tremor may well be a good marker for disease heterogeneity.

It has been suggested that parkin disease is more symmetric than typical late onset PD on the basis of autopsy data and functional imaging (Scherfler, Khan *et al.* 2004) (Sasaki, Shirata *et al.* 2004) . In general terms genetically mediated diseases are usually symmetric (e.g. hereditary spastic paraparesis), presumably reflecting a homogenous effect of a pathogenic genetic mutation. From these data, there was no evidence to

suggest that YOPD was more symmetrical clinically than LOPD. However, our method of measuring clinical symmetry involved comparing side by side variation in UPDRS scores which is likely to be influenced by the non-linear nature of the UPDRS motor score and by the examiner's expectation that PD is an asymmetric disease. A more accurate measure may be made using surrogate markers such as neuro-imaging, or by using quantitative motor measures such as timed tap tests. It is likely that our data do not portray an accurate representation of disease symmetry and progression, and that prospective follow up of incident cases would more accurately identify whether YOPD cases became more symmetrical earlier on in their disease course than LOPD. Such a study (Giovannini, Piccolo *et al.* 1991) looking at time to bilateral clinical involvement suggested that YOPD affects both sides of the body earlier in the disease course. This is not quite the same as saying LOPD remains more asymmetric for longer nor is it the same as saying YOPD has a more aggressive disease course as suggested by the authors. Some dopamine transporter studies have however suggested earlier bilateral involvement of the dopaminergic pathways in YOPD but this may not necessarily correspond to the clinical picture. The basis of asymmetry in PD is unknown but may well reflect a fundamental aspect of the disease pathogenesis.

A third of our cohort reported the presence of dystonic symptoms. Twenty percent of the YOPD group reported dystonia at onset and a further 11 % within the first two years of first cardinal motor symptom. This is very likely an underestimation of the true prevalence of dystonia amongst PD patients as this study had relied on patients recognising this phenomenon and self reporting symptoms at interview. Asymptomatic dystonic posturing is likely to go unnoticed by most patients and may only be evident on examination. Previous published reports quote a figure of between 14-57% of dystonia at onset in YOPD (Table 2-5). Similarly, 30% of our YOPD cohort reported L-dopa related off period dystonia. Previous published figures are reported as 30-59% (Quinn, Critchley *et al.* 1987; Gibb and Lees 1988). However, the majority of these published figures are based on specialist clinic series and are likely to represent a high percentage of atypical YOPD cases that have been referred for specialist management. Less than 3% of the LOPD group reported dystonia of any kind and again this is slightly lower than published figures which range from 0-10% (Table 2-5).

A standardised method to assess dystonia in PD has not been established to date and one relies on the patients' awareness of symptoms to establish its presence. It is possible that these data are confounded by an increased awareness of subtle symptoms by younger onset patients. It is clear from examining these patients that a degree of dystonic posturing is extremely common but the functional and prognostic relevance of this in asymptomatic patients are unclear.

6.4.2 Response to treatment

Reported rates of dyskinesia vary, but a recent analysis of previously published data suggested that there is a 40% risk of developing dyskinesia after for 4-6 years of L dopa treatment (Ahlskog and Muenter 2001). About 20% of our PD cohort reported dyskinesias to be present which, considering that the mean disease duration was 9 years, is surprisingly low. This may reflects active observation and recording of dyskinesia in pharmaceutical studies with multiple follow up visits. Significantly more dyskinesias were reported by patients with YOPD and this rate fell with increasing age at onset. These data reflect previous studies. Many previous studies have reported the frequency of dyskinesia in YOPD but few have reported the impact on quality of life. In those with dyskinesias, the YOPD group were affected for larger proportions of the waking day. YOPD reported more disruption to their daily quality of life by the presence of dyskinesia as scored by the Lang and Fahn ADL QOL scale.

To this day, controversy exists as to whether the occurrence of dyskinesia and motor fluctuations is primarily related to PD itself or its treatment. It has been common practice to delay L DOPA treatment for as long as possible, especially in YOPD patients due to reports from small clinic series studies suggesting YOPD patients develop dyskinesias earlier than LOPD patients. One such study carefully corrected for disease and treatment duration in 25 YOPD and 25 LOPD patients (Kostic, Przedborski *et al.* 1991). Gomez *et al* performed retrospective analysis and acute L DOPA challenge in 34 YOPD (onset <40) and 34 LOPD (onset >60) and found that motor fluctuations and dyskinesias were more common in YOPD. The latency to L DOPA response during the acute challenge was no different between YOPD and LOPD patients. From the retrospective analysis, it was found that dyskinesias developed earlier in YOPD patients, within 4 years of disease onset and 2 years of treatment onset (compared to 5 and 4 years in LOPD) (Gomez

Arevalo, Jorge *et al.* 1997). These authors also described a difference in dyskinesia type between YOIPD and LOPD, noting that ballistic, dystonic, off period and biphasic dyskinesia were more common in YOPD. This led the authors to conclude that this was due to an age related phenomenon rather than due to disease heterogeneity.

Schrag *et al* concluded from their community based study of 124 patients with PD that motor fluctuations were strongly related to disease duration and L DOPA dose and that dyskinesias were related to treatment duration (Schrag and Quinn 2000).

Our data confirm the important effect of age at onset on the development of dyskinesias. Multivariate analysis suggests that the major risk factors are independently associated with the risk of developing dyskinesias. However, it is important to note that the cumulative L DOPA dose was not calculated, only the total daily dose of L DOPA at time of the assessment.

6.4.3 Limitations

This study was limited by its retrospective nature. It would have been more representative to prospectively follow up cases from disease onset to study development of bilateral involvement. However, prospective follow up of cases to allow for any meaningful data would require long follow periods. With the limited resources and time assigned to this project, a retrospective assessment of a large number of PD patients was a reasonable approximation.

The frequencies of both dystonia and dyskinesias in this study were reliant on patient self report at interview and so are likely to be underestimates. It is possible that this may be affected differentially by age or age at onset. Younger patients may be less likely to accept dystonia as a normal feature of ageing as older patients may. YOPD patients are more likely to be referred to a specialist clinic where physicians and therefore patients may be more aware of the presence of both dystonia and dyskinesias. There are no standardised methods to assess frequencies of dystonia in PD and the UPDRS part IV relies on patient self report for the presence of dyskinesia. It was evident in the clinical assessment that often patients were unaware of mild non intrusive dyskinesias.

At the time the study was commenced the standard UPDRS (Unified Parkinson's Disease Rating Scale) was the most commonly used research tool to assess motor state. However, the nature of the scale is very insensitive. The UPDRS motor scale scores each component of the examination between 0 and 4 which are to some degree broadly dependant on the examiner. Since this study started, a new modified UPDRS has been designed which is far more detailed and may leave less scope for inter-examiner variability.

6.4.4 Strengths

The aim of this study was to compare YOPD and LOPD patients from a community based cohort. Although only a third of the patients were ascertained from the prevalence study, there was no significant difference between the prevalent and non prevalent cases.

A large number of patients with PD were assessed with a range of onset ages. All patients were assessed using standardised proformas and where available, validated scales were used e.g. UPDRS, Lang and Fahn ADL scale. Since the commencement of this study, new standardised scales have been published and validated which may have been utilised had they been developed in time for this study.

All clinical assessments were performed by one examiner. Therefore there was no concern regarding inter-rater variability. However, as the assessments were performed over a two year period there may have been an element of intra-rater variation namely a learning effect. All clinical assessments were video taped and it can be possible to assess this issue although this was not done for this thesis.

6.5 Conclusions

Significant differences are seen in the profile of motor symptoms of YOPD and LOPD suggesting the differentiation of clinical sub-types of PD separated by age at onset. YOPD commonly present with symptoms related to akinesia and rigidity, have slower disease progression and higher frequencies of both dystonia and dyskinesia. These findings are in keeping with previously published data. This information can help to further classify PD by investigating clinico-genetic correlations. On a more practical

level, advice regarding earlier recognition and diagnosis of YOPD and tailoring management of medication based on age at onset can be developed from these data.

Chapter 7 Conclusion

7.1 Major Findings

This study provides new data on patients with YOPD. Our data suggest temporal and geographical stability in the prevalence of PD over the past 42 years. This observation was made possible by performing analysis of the available raw data from these previous studies and highlights the usefulness of standardising methodologies in publishing data, for example publishing data for 5 year age strata.

The methods of case ascertainment are crucial in epidemiological studies and this has become apparent in this work. Neither primary nor secondary care alone provided accurate and complete data on prevalent cases. As discussed, our data cannot explain the variation in prevalence between rural North Wales and Cardiff. The ideal way to overcome this would be to use identical methodology in rural and urban settings.

Our prevalence estimates are in keeping with the weighted average from previously published data. Our crude prevalence estimate was 130 per 10^5 (95% CI 117,144) and age standardised prevalence using the 1997 England and Wales population was 142 per 10^5 (95% CI 128, 156). Gender differences observed in this study suggest male preponderance, with a male to female prevalence ratio of 1.43 (95% CI 1.17, 1.76, p=0.001). The mean age at onset of our cohort was 68.6 years (95%CI 67.5, 69.8), for men 67.7 years (95% CI 66.0, 69.3) and for women 69.9 years (95%CI 68.1, 71.4).

Our study has identified a substantial prevalence of YOPD. These data should encourage the increase in awareness of PD developing at a younger than usual age and help shape appropriate health care services. A major outcome of this study has been engaging patients, physicians and PD nurse specialists in PD research in the South Wales area. We have engaged in a series of patient and carer educational activities which have assisted in research and aided in increasing awareness of YOPD.

Although this study was primarily designed to be a community based study the low recruitment rates required supplementation from secondary care resources, however

analysis showed there were no significant differences between the cases from the prevalence study and the secondary care group. Our data have shown significant heterogeneity in the clinical features of PD by age at onset, both in the motor and non motor aspects of the disease.

Our data on non motor features suggest a different pattern of disease in YOPD and LOPD. The significance of this is uncertain but could be explored further by clinico-pathological and clinico-genetic correlations. Surprisingly, we have robust evidence to support the association of tremor with age at onset of PD suggesting the pattern of neurodegeneration may differ according to age at onset. We have identified a major association between dystonia and YOPD and again this must relate to fundamental biological differences. Though treatment related dyskinesias are commoner in YOPD, we have evidence to suggest that the development of dyskinesias can be predicted by four independent factors. These are age at onset, disease duration, dose of L DOPA and treatment duration. Although these are well recognised to be important, few studies have analysed their individual contributions.

7.2 Alternative Approaches

The information gathered from both the prevalence study and the comparative study of clinical differences of YOPD and LOPD has added to the existing knowledge base of YOPD. There are, however, several practical issues which could be improved if the study were to be performed again.

7.2.1 Prevalence Study

The initial recruitment of general practitioners could have been more efficient and focussed. General practitioners, like many busy professionals, may ignore non-urgent requests for assistance with research. The original mail shot to the head of practice may not have been the most effective way of introducing the study to the primary care setting. It became obvious as the study progressed that the practice manager was the best person to liaise with when requesting participation of the practice in the study. Initial contact by telephone, then an e-mail outlining the conversation including salient points of the study protocol and project paperwork followed up by a telephone call was probably the most effective method of recruiting practices. It was easier to target batches of specific

practices and concentrate contact rather than to involve all practices at the same time, as was the original strategy.

Some practices in Cardiff did not join the study- we reached only 83% participation (45 out of 54 practices). But the population denominator covered 96% of the Cardiff population, as the bigger practices were recruited, and subsequently this was the second largest prevalence study in the UK to date. However the recruitment period spanned fourteen months and a more efficient strategy may have accelerated this phase.

The study design did not fully capture individual case tracing from different referral sources. This was because patients were only given a unique study code after duplicate records were discarded in primary care. Our initial code used was a per individual code, but in order to maximise information from this initial phase we should have used a "potential case notification code", related to case source with each individual associated with multiple case identification codes.

During the pilot searches, it would have been better to assess the accuracy of the individual search terms by using examination of the cases as the gold standard for diagnostic accuracy. However, in the interest of time, we could only be as accurate as the best recorded GP or secondary care clinic letter available.

We were unable to explain why some cases had been missed by the GP electronic database searches but had been identified via secondary care sources although registered with the GP practices who participated in the prevalence study. This was determined by the sequence of primary care screen, followed by secondary care screen. It may have been better to have had a list of cases known to secondary care registered at each practice, before visiting the practice to perform the GP database search in order to try to identify why cases were not pulled up by the search protocol. Unfortunately, at that time there was no efficient way of identifying cases from secondary care, so attempting to do this would have been more time consuming and delayed the start of the prevalence study. It appears, however, that reasonable ascertainment using both sources was reached.

The prevalence of dementia was very low in our cohort of PD patients. This was likely due to the selection bias introduced by the exclusion criteria used at the GP screening stage. Once patients were identified as potential cases following the electronic database search and case note review, one GP per practice was asked to screen the list of patients to identify and exclude those patients they felt inappropriate to contact. The exclusion criteria included severe dementia, it may be that some GPs excluded patients perhaps who may have been suitable to be included in the study. Evidence for this was illustrated by one example where a patient was excluded by their GP because they were deemed to have severe dementia but this same patient was referred into the study by their secondary care physician and did not have significant cognitive impairment at assessment. Although patients such as this would have been included in the prevalence estimate, the exclusion of dementia patients from clinical assessment has undoubtedly led to an underestimation of the true prevalence of dementia in this study cohort and suggests that GPs use of dementia as an exclusion label may not be diagnostically accurate.

This prevalence study is the second largest in the UK. However, there is a trade off between study denominator size and degree of detailed screening possible. Ideally we would have liked to have examined all patients presenting with tremor for evidence of parkinsonism looking for undiagnosed PD as in the study conducted by Schrag *et al* (Schrag, Ben-Shlomo *et al.* 2000). Schrag *et al* suggested that approximately 20% of patients with Parkinson's disease who had already come to medical attention had not been diagnosed as such but fulfilled Queen Square Brain Bank criteria at assessment (Schrag, Ben-Shlomo *et al.* 2002). This was reiterated by the Norwegian study screening for PD in nursing homes (Larsen 1991).

The initial basic screening questionnaire (BSQ) was designed to be administered as a screening tool incorporating some diagnostic questions from the Brain Bank Criteria. Its purpose was threefold - to screen patients with diagnoses other than PD, to obtain written consent to gain access to medical records, and to determine self reported age at onset. The age at onset was initially part of the inclusion criteria as the protocol first intended to compare patients with onset before 55 and those with onset over 70, but this was changed early into the data collection phase to include all ages at onset because of rate of recruitment. By collecting data on patients with a spectrum of onset ages, it was possible

to investigate for a continuous relationship between age at onset and clinical features as well as bimodal differences.

Our response rate from the prevalence study was disappointing, almost 40% of those invited did not respond at all (although of the 62% who did respond, 75% agreed to participate in the study).

7.2.2 YOPD vs. LOPD study

The number of prevalent patients agreeing to attend for clinical assessment was lower than expected. Out of the 380 cases identified as prevalent cases, only about one third attended for clinical assessment. It was envisaged that only a small number of YOPD patients would be recruited for clinical assessment from the prevalence study and so secondary care sources were involved primarily to ascertain further YOPD cases. However, because of the low participation rate of all onset ages, secondary care sources outside Cardiff were used to supplement cases of all onset ages.

Non Motor Symptoms

As the emphasis of the comparative study was to report frequencies of a wide spectrum of clinical features in a large number of PD patients by age at onset, it was not possible in the time frame of the study to look at any one feature in a great deal of depth. There is therefore a great deal of potential for further study within this cohort.

For the majority of the non motor symptoms, frequencies were calculated based on self report by the patients when directly questioned. Some standardised scales were also used such as the BDI, Epworth and MMSE. Clearly many of the clinical features assessed would benefit from more detailed assessment. For example, the use of a standardised clinical test, such as the University of Pennsylvania Smell Identification Tests (UPSIT) smell tests, will be more accurate than patient interview. There may be a differential reporting of hyposmia by age at onset as loss of smell tends to be regarded as part of the normal ageing process and so may be under reported in the older age groups. This may confound the assessment of non-motor features by interview.

There is growing awareness of a wide range of non-motor features affecting patients with PD. Further non motor features not studied in this thesis include urinary dysfunction, sexual dysfunction, thermoregulatory dysfunction, orthostatic hypotension, cardiovascular involvement, psychosis, anxiety, apathy, panic attacks, impulse control disorders, obsessive compulsive disorder, dopamine dysregulation disorder and sleep apnoea.

The MMSE was used as a screen for cognitive dysfunction. Although this is useful as a brief clinical screening tool, it does not provide any detailed assessment of frontal dysexecutive and visuo-perceptual function, known to be important aspects of cognitive impairment in PD. Studying incident cases and assessing the influence of disease duration prospectively in YOPD and LOPD may be revealing. The influence of age on cognitive function should also be taken into account. Ideally this should be done by comparing cognitive tests in PD patients and age matched controls.

Motor Clinical Features

Ideally, assessment of symmetry is best done in prospective way, on an incident cohort of PD patients. In this study, because the patients were established cases with varying disease durations the best estimate could only be performed at a contemporary assessment. This is likely to not represent the true disease pattern in these patients as the point at which symmetry develops is probably obscured with advancing disease duration and is likely to be missed in retrospective analysis. The UPDRS is likely to obscure differences in symmetry because of the categorical nature of the scale and the expectation of asymmetry by the examiner, and alternative methods of rating disease symmetry would be more helpful.

The assessment of dystonia in this study relied on self report when cases were directly questioned. This is dependant on the patients being aware and recognising the symptoms. Dystonia could have been more objectively assessed. It may have been possible to educate patients by giving them standardised training in recognising symptoms before the clinic assessment. Videotape recordings of each assessment were made which could be used to determine the presence of dystonic posturing but of course this only represents a snap shot of each patient's motor state at any given time. PD patients can be in a dynamic

variable motor state over course of the day and so relying purely on the video recording taken at a one off clinic visit will undoubtedly underreport the presence of dystonia.

A large amount of additional data that were not reported in this thesis have been collected. This includes data on family history, quality of life and environmental exposures. However, interpretation of these data are largely reliant on the comparison with control data. The recruitment of controls was more complicated and time consuming than first realised and so this part of the project could not be completed in the time frame for this thesis. We took the approach of seeking patient matched controls from primary care, asking the national body, Health Solutions Wales to identify suitable controls. This was a time-consuming approach which to date has yielded a low response rate.

7.3 Impact of Study Findings on the management of YOPD

Awareness of PD starting at an earlier than usual age is increasing and recognition of the disease both by people with PD and by health care professionals, aids earlier diagnosis. Patients with YOPD may present with atypical features including prominent dystonia and prominent akinetic rigid symptoms. Though the incidence of YOPD remains relatively low making it a condition that the average general practitioner is rarely likely to see a lot of, the impact of accurate and early diagnosis to patients is significant. Educating both the general population and physicians regarding frequencies of these presenting features will improve diagnostic speed and accuracy, channelling diagnostic tests and referral to the appropriate health care services. A big element contributing to anxiety in symptomatic undiagnosed patients is the uncertainty of diagnosis at presentation, and earlier recognition of symptoms will help to improve this.

In addition to reducing delay in diagnosis, identifying specific healthcare issues associated with YOPD should provide better care for these patients. Studying the frequencies of treatment related complications will help to inform both the patient and physician to reaching an educated rationale in treatment regimes. Understanding that YOPD may respond better to L DOPA treatment but involve development of earlier treatment related complications can influence individual treatment choices tailored to each patients unique needs. This is obviously dependant on the financial, social and

psychological demands of the patient and one can imagine how this may differ with age, family commitments and employment status. A person in their thirties or forties with a young family to support may wish to start L DOPA medication early and benefit from better motor control during their working years whilst risking the development of dyskinesias, whereas an older individual who perhaps may be retired may prefer to avoid treatment related complications in doing so preferring to have suboptimal motor control which may be adequate for their pace of life. Information on the risk of developing treatment related complication and what impact these may have on quality of life are crucial to making as informed decision as possible regarding treatment strategies.

The identification of non motor symptoms has become a major research focus over the past few years. They are an important aspect of PD management and cause a great deal of morbidity, which was previously under-recognised by the medical profession. PD was once thought to be a predominantly dopaminergic motor disorder, the symptoms of which were largely responsive to L DOPA treatment. It is becoming rapidly understood that the non dopaminergic systems are involved in a spectrum of non motor features, which are common in PD when looked for and cause a great deal of distress to patients. These symptoms do not respond well to L DOPA treatment but require alternative, maybe non pharmacological, interventions. The emphasis should be to address these issues, as often they cause the majority of morbidity in the later stages of the disease, and may be helped by simple measures. The differing profiles of non motor symptoms in YOPD and LOPD should be acknowledged to help tailor specific management issues to PD patients according to age at onset. For example, it is important to recognise the high prevalence of depression and sleep disturbance in the YOPD population, both of which cause deterioration in quality of life but can be managed appropriately if recognised by patients and physicians.

The recognition of premotor symptoms will become important in the era of neuroprotection. Again the differing profile between YOPD and LOPD is important to bear in mind. Recent suggestions that the triad of hyposmia, REM sleep behavioural disorder and constipation may be a risk factor for developing PD will impact on how screening for PD may occur, but our study suggests that this triad may only be relevant for LOPD.

7.4 Future Directions

Further analysis of our data could include cluster or factor analysis in an attempt to find clinical subtypes of PD, not defined by age at onset. A study looking at an unselected cohort of PD patients in the early stages of the disease demonstrated evidence of heterogeneity by performing cluster analysis (Lewis, Foltynie *et al.* 2005). This study identified 4 distinct subgroups of PD using the data driven approach, younger age at onset (<50) being one. This group was found to have slow disease progression, mild motor symptoms, no cognitive impairment and lower depression ratings. Our work collaborates some of these findings but not all. We found patients with YOPD had less cognitive impairment but higher depression ratings.

It seems likely that genetic analysis will clarify disease heterogeneity. However, surprisingly further studies looking at the clinical features of parkin positive and negative patients found no clinical way of distinguishing these groups (Lohmann, Thobois et al. 2009). This suggests that genetic heterogeneity may be less important than biological age in explaining clinical heterogeneity in PD. Genetic analysis of the cohort described in this thesis is ongoing and will provide a valuable correlation with the clinical data. Epidemiological data support the identification of further genetic factors in YOPD. Marder *et al* (Marder, Levy *et al.* 2003) report that siblings of YOPD patients have a 8 fold increased risk of developing PD as compared to siblings of controls. This increased risk of familial aggregation was also found by others (Payami, Zareparsi *et al.* 2002; Rocca, McDonnell *et al.* 2004).

During the period of this study, a large amount of additional data were collected which await matched control data. The data collection for general population control is still underway and will provide control comparison data on quality of life, environmental exposures, daytime somnolence and depression.

All patients were also offered the opportunity to donate their brains to the Queen Square Brain Bank at the University College London/Queen Square. Although only a few

patients (10%) recruited in this study have signed consent for donation to date, all have been approached about the importance of pathological confirmation of diagnosis and how this aids further understanding of PD. If a substantial number of patients subsequently consented to donate their brains for pathological examination it may be possible to examine for clinico-pathological correlations in this cohort. The relative importance of Lewy body and non-Lewy body disease in YOPD remains uncertain.

A further goal for future work is the longitudinal follow up of disease progression and drug responsiveness and development of drug related complications. A much more accurate picture of these aspects can only be gained from prospective study. Objective measure of disease progression performed at two points in time to can be used to estimate disease progression prospectively.

In addition, there is further scope to engage in more in-depth evaluation of areas of interest identified in this work. Detailed cognitive assessments, autonomic dysfunction, non motor aspects, sleep disturbances and psychiatric complications of dopamine replacement therapy are but a few possible areas for further study.

Although there are improvements that could have been made to the study design and there are future directions to be explored, this study has provided major insights into YOPD and paved the way for future research into this fascinating condition.

References

(2001). "Evaluation of dyskinesias in a pilot, randomized, placebo-controlled trial of remacemide in advanced Parkinson disease." Arch Neurol **58**(10): 1660-8.

Aarsland, D., K. Andersen, et al. (2003). "Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study." Arch Neurol **60**(3): 387-92.

Aarsland, D., J. P. Larsen, et al. (1999). "Range of neuropsychiatric disturbances in patients with Parkinson's disease." J Neurol Neurosurg Psychiatry **67**(4): 492-6.

Aarsland, D., E. Tandberg, et al. (1996). "Frequency of dementia in Parkinson disease." Arch Neurol **53**(6): 538-42.

Abbott, R. D., H. Petrovitch, et al. (2001). "Frequency of bowel movements and the future risk of Parkinson's disease." Neurology **57**(3): 456-62.

Abbott, R. D., G. W. Ross, et al. (2005). "Excessive daytime sleepiness and subsequent development of Parkinson disease." Neurology **65**(9): 1442-6.

Abele, M., A. Riet, et al. (2003). "Olfactory dysfunction in cerebellar ataxia and multiple system atrophy." J Neurol **250**(12): 1453-5.

Ahlskog, J. E. (2007). "Beating a dead horse: dopamine and Parkinson disease." Neurology **69**(17): 1701-11.

Ahlskog, J. E. and M. D. Muenter (2001). "Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature." Mov Disord **16**(3): 448-58.

Ansari, K. A. and A. Johnson (1975). "Olfactory function in patients with Parkinson's disease." J Chronic Dis **28**(9): 493-7.

Antonini, A., R. M. Moresco, et al. (2002). "Striatal dopaminergic denervation in early and late onset Parkinson's disease assessed by PET and the tracer [11C]FECIT: preliminary findings in one patient with autosomal recessive parkinsonism (Park2)." Neurol Sci **23 Suppl 2**: S51-2.

Apaydin, H., J. E. Ahlskog, et al. (2002). "Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response." Arch Neurol **59**(1): 102-12.

Ashraf, W., R. F. Pfeiffer, et al. (1997). "Constipation in Parkinson's disease: objective assessment and response to psyllium." Mov Disord **12**(6): 946-51.

Barbeau, A. and E. Pourcher (1982). "New data on the genetics of Parkinson's disease." Can J Neurol Sci **9**(1): 53-60.

Bateman, D. E., K. Levett, et al. (1999). "Sleep benefit in Parkinson's disease." J Neurol Neurosurg Psychiatry **67**(3): 384-5.

Beck, A. T., C. H. Ward, et al. (1961). "An inventory for measuring depression." Arch Gen Psychiatry **4**: 561-71.

Ben-Shlomo, Y. (1996). "How far are we in understanding the cause of Parkinson's disease?" J Neurol Neurosurg Psychiatry **61**(1): 4-16.

Ben-Shlomo, Y. and M. G. Marmot (1995). "Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology?" J Neurol Neurosurg Psychiatry **58**(3): 293-9.

Biggins, C. A., J. L. Boyd, et al. (1992). "A controlled, longitudinal study of dementia in Parkinson's disease." J Neurol Neurosurg Psychiatry **55**(7): 566-71.

Birkmayer, W., P. Riederer, et al. (1979). "Distinction between benign and malignant type of Parkinson's disease." Clinical Neurology and Neurosurgery **81**(3): 158-64.

Bozi, M. and K. P. Bhatia (2003). "Paroxysmal exercise-induced dystonia as a presenting feature of young-onset Parkinson's disease." Mov Disord **18**(12): 1545-7.
Braak, H., J. R. Bohl, et al. (2006). "Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered." Mov Disord **21**(12): 2042-51.
Braak, H., K. Del Tredici, et al. (2003). "Staging of brain pathology related to sporadic Parkinson's disease." Neurobiol Aging **24**(2): 197-211.
Brewis, M., D. C. Poskanzer, et al. (1966). "Neurological disease in an English city." Acta Neurol Scand **42**: Suppl 24:1-89.
Brooks, D. J. (2000). "Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease." J Neurol **247 Suppl 2**: II11-8.
Burn, D. J. (2002). "Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease." Mov Disord **17**(3): 445-54.
Caslake, R., J. N. Moore, et al. (2008). "Changes in diagnosis with follow-up in an incident cohort of patients with parkinsonism." J Neurol Neurosurg Psychiatry **79**(11): 1202-7.
Chaudhuri, K. R., D. G. Healy, et al. (2006). "Non-motor symptoms of Parkinson's disease: diagnosis and management." Lancet Neurol **5**(3): 235-45.
Chaudhuri, K. R., P. Martinez-Martin, et al. (2006). "International Multicenter Pilot Study of the First Comprehensive Self-Completed Nonmotor Symptoms Questionnaire for Parkinson's Disease: The NMSQuest Study." Movement Disorders **21**(7): 916-923.
Cooper, J. A., H. J. Sagar, et al. (1991). "Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability." Brain **114 (Pt 5)**: 2095-122.
Cummings, J. L. (1992). "Depression and Parkinson's disease: a review." Am J Psychiatry **149**(4): 443-54.
Currie, L. J., J. P. Bennett, Jr., et al. (1997). "Clinical correlates of sleep benefit in Parkinson's disease." Neurology **48**(4): 1115-7.
de Jong, G. J., J. D. Meerwaldt, et al. (1987). "Factors that influence the occurrence of response variations in Parkinson's disease." Ann Neurol **22**(1): 4-7.
de Lau, L. M. and M. M. Breteler (2006). "Epidemiology of Parkinson's disease." Lancet Neurol **5**(6): 525-35.
de Rijk MC, T. C., Breteler MM (1997). "Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study." J Neurol Neurosurg Psychiatry **62**: 10-15.
Diamond, S. G., C. H. Markham, et al. (1989). "Effect of age at onset on progression and mortality in Parkinson's disease." Neurology **39**(9): 1187-90.
Doty, R. L., M. B. Stern, et al. (1992). "Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease." J Neurol Neurosurg Psychiatry **55**(2): 138-42.
Dubois, B., B. Pillon, et al. (1990). "Age-induced cognitive disturbances in Parkinson's disease." Neurology **40**(1): 38-41.
Ebmeier, K. P., S. A. Calder, et al. (1990). "Clinical features predicting dementia in idiopathic Parkinson's disease: a follow-up study." Neurology **40**(8): 1222-4.
Elizan, T. S., H. Sroka, et al. (1986). "Dementia in idiopathic Parkinson's disease. Variables associated with its occurrence in 203 patients." J Neural Transm **65**(3-4): 285-302.

Emre, M. (2003). "Dementia associated with Parkinson's disease." Lancet Neurol **2**(4): 229-37.
Factor, S. A., T. McAlarney, et al. (1990). "Sleep disorders and sleep effect in Parkinson's disease." Mov Disord **5**(4): 280-5.
Fahn, S., R. L. Elton, et al. (1987). Unified Parkinson's Disease Rating Scale. In: Recent developments in Parkinson's disease. Florham Park, NJ, Macmillan Healthcare Information.
Farrer, M., P. Chan, et al. (2001). "Lewy bodies and parkinsonism in families with parkin mutations." Ann Neurol **50**(3): 293-300.
Farrer, M., J. Kachergus, et al. (2004). "Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications." Ann Neurol **55**(2): 174-9.
Fearnley, J. M. and A. J. Lees (1991). "Ageing and Parkinson's disease: substantia nigra regional selectivity." Brain **114 (Pt 5)**: 2283-301.
Fishman, P. S. (2008). "Paradoxical Aspects of Parkinsonian Tremor." Movement Disorders **23**(2): 168-173.
Folstein, M. F., S. E. Folstein, et al. (1975). ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res **12**(3): 189-98.
Foltynie, T., C. E. Brayne, et al. (2004). "The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study." Brain **127**(Pt 3): 550-60.
Friedman, A. (1994). "Old-onset Parkinson's disease compared with young-onset disease: clinical differences and similarities." Acta Neurol Scand **89**(4): 258-61.
Gershanik (1988). Parkinson's disease and movement disorders. Baltimore, Urban & Schwarzenberg.
Gershanik, O. S. and A. Leist (1987). "Juvenile onset Parkinson's disease." Adv Neurol **45**: 213-6.
Gershanik, O. S. and T. G. Nygaard (1990). "Parkinson's disease beginning before age 40." Adv Neurol **53**: 251-8.
Gibb, W. R. and A. J. Lees (1988). "A comparison of clinical and pathological features of young- and old-onset Parkinson's disease." Neurology **38**(9): 1402-6.
Gibb, W. R. and A. J. Lees (1988). "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease." J Neurol Neurosurg Psychiatry **51**(6): 745-52.
Giovannini, P., I. Piccolo, et al. (1991). "Early-onset Parkinson's disease." Mov Disord **6**(1): 36-42.
Goetz, C. G., C. M. Tanner, et al. (1988). "Risk factors for progression in Parkinson's disease." Neurology **38**(12): 1841-4.
Gomez Arevalo, G., R. Jorge, et al. (1997). "Clinical and pharmacological differences in early- versus late-onset Parkinson's disease." Mov Disord **12**(3): 277-84.
Gonera, E. G., M. van't Hof, et al. (1997). "Symptoms and duration of the prodromal phase in Parkinson's disease." Mov Disord **12**(6): 871-6.
Granerus, A. K., Carlsson A, Svanborg A (1979). "The ageing neurone - influence on symptomatology and therapeutic response in Parkinson's syndrome." Adv Neurol **24**: 327-334.
Greenamyre, J. T. and T. G. Hastings (2004). "Biomedicine. Parkinson's--divergent causes, convergent mechanisms." Science **304**(5674): 1120-2.
Habermann-Little, B. (1991). "An analysis of the prevalence and etiology of depression in Parkinson's disease." J Neurosci Nurs **23**(3): 165-9.
Hantz, P., G. Caradoc-Davies, et al. (1994). "Depression in Parkinson's disease." Am J Psychiatry **151**(7): 1010-4.

Hardy, J., H. Cai, et al. (2006). "Genetics of Parkinson's disease and parkinsonism." Ann Neurol **60**(4): 389-98.
Hawkes, C. (2003). "Olfaction in neurodegenerative disorder." Mov Disord **18**(4): 364-72.
Hayashi, S., K. Wakabayashi, et al. (2000). "An autopsy case of autosomal-recessive juvenile parkinsonism with a homozygous exon 4 deletion in the parkin gene." Mov Disord **15**(5): 884-8.
Hely, M. A., J. G. Morris, et al. (1995). "Age at onset: the major determinant of outcome in Parkinson's disease." Acta Neurol Scand **92**(6): 455-63.
Henderson, J. M., Y. Lu, et al. (2003). "Olfactory deficits and sleep disturbances in Parkinson's disease: a case-control survey." J Neurol Neurosurg Psychiatry **74**(7): 956-8.
Hershey, L. A., B. J. Feldman, et al. (1991). "Tremor at onset. Predictor of cognitive and motor outcome in Parkinson's disease?" Arch Neurol **48**(10): 1049-51.
Hietanen, M. and H. Teravainen (1988). "The effect of age of disease onset on neuropsychological performance in Parkinson's disease." J Neurol Neurosurg Psychiatry **51**(2): 244-9.
Hobson JP, M. R. (1999). "A Descriptive Epidemiological Study of Parkinson's disease in North Wales." Age Ageing **28 suppl 1**: 63.
Hobson, P. and J. Meara (2004). "Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom." Mov Disord **19**(9): 1043-9.
Hoehn, M. M. and M. D. Yahr (1967). "Parkinsonism: onset, progression and mortality." Neurology **17**(5): 427-42.
Huber, S. J., G. W. Paulson, et al. (1988). "Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease." J Neurol Neurosurg Psychiatry **51**(6): 855-8.
Hughes, A. J., S. E. Daniel, et al. (2002). "The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service." Brain **125**(Pt 4): 861-70.
Hughes, A. J., S. E. Daniel, et al. (1992). "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases." J Neurol Neurosurg Psychiatry **55**(3): 181-4.
Hughes, A. J., S. E. Daniel, et al. (2001). "Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease." Neurology **57**(8): 1497-9.
Iranzo, A., J. L. Molinuevo, et al. (2006). "Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study." Lancet Neurol **5**(7): 572-7.
Ishihara, L. and C. Brayne (2006). "A systematic review of depression and mental illness preceding Parkinson's disease." Acta Neurol Scand **113**(4): 211-20.
Ishihara, L. S., A. Cheesbrough, et al. (2007). "Estimated life expectancy of Parkinson's patients compared with the UK population." J Neurol Neurosurg Psychiatry **78**(12): 1304-9.
Jankovic, J., M. McDermott, et al. (1990). "Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group." Neurology **40**(10): 1529-34.
Jankovic, J., Tolosa E. (1993). Parkinson's disease and Related disoreders. BAltimore, Williams & Wilkins.
Jellinger, K. (1987). The pathology of parkinsonism. London, Butterworths.

Jenkinson, C., S. Stewart-Brown, et al. (1999). "Assessment of the SF-36 version 2 in the United Kingdom." J Epidemiol Community Health **53**(1): 46-50.
Johns, M. W. (1991). "A new method for measuring daytime sleepiness: the Epworth sleepiness scale." Sleep **14**(6): 540-5.
Johnson, W. G., S. E. Hodge, et al. (1990). "Twin studies and the genetics of Parkinson's disease--a reappraisal." Mov Disord **5**(3): 187-94.
Josephs, K. A., J. Y. Matsumoto, et al. (2006). "Benign tremulous parkinsonism." Arch Neurol **63**(3): 354-7.
Kaye, J., H. Gage, et al. (2006). "Excess burden of constipation in Parkinson's disease: a pilot study." Mov Disord **21**(8): 1270-3.
Khan, N. L., E. Graham, et al. (2003). "Parkin disease: a phenotypic study of a large case series." Brain **126**(Pt 6): 1279-92.
Kidron, D. and E. Melamed (1987). "Forms of dystonia in patients with Parkinson's disease." Neurology **37**(6): 1009-11.
Klein, C., K. Lohmann-Hedrich, et al. (2007). "Deciphering the role of heterozygous mutations in genes associated with parkinsonism." Lancet Neurol **6**(7): 652-62.
Koller, W. C. and A. E. Lang (1987). "Age of onset of Parkinson's disease." Can J Neurol Sci **14**(2): 179-80.
Kostic, V., S. Przedborski, et al. (1991). "Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease." Neurology **41**(2 (Pt 1)): 202-5.
Kostic, V. S., S. R. Filipovic, et al. (1994). "Effect of age at onset on frequency of depression in Parkinson's disease." J Neurol Neurosurg Psychiatry **57**(10): 1265-7.
Kumar, N., J. A. Van Gerpen, et al. (2005). "Levodopa-dyskinesia incidence by age of Parkinson's disease onset." Mov Disord **20**(3): 342-4.
Larsen, J. P. (1991). "Parkinson's disease as community health problem: study in Norwegian nursing homes. The Norwegian Study Group of Parkinson's Disease in the Elderly." Bmj **303**(6805): 741-3.
Lauterbach, E. C., A. Freeman, et al. (2004). "Differential DSM-III psychiatric disorder prevalence profiles in dystonia and Parkinson's disease." J Neuropsychiatry Clin Neurosci **16**(1): 29-36.
Lee, C. S., M. Schulzer, et al. (1994). "Clinical observations on the rate of progression of idiopathic parkinsonism." Brain **117 (Pt 3)**: 501-7.
Leentjens, A. F., M. Van den Akker, et al. (2003). "Higher incidence of depression preceding the onset of Parkinson's disease: a register study." Mov Disord **18**(4): 414-8.
Lees, A. J., N. A. Blackburn, et al. (1988). "The nighttime problems of Parkinson's disease." Clin Neuropharmacol **11**(6): 512-9.
Lewis, S. J., T. Foltynie, et al. (2005). "Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach." J Neurol Neurosurg Psychiatry **76**(3): 343-8.
Lieberman, A., M. Dziatolowski, et al. (1979). "Dementia in Parkinson Disease." Ann Neurol **6**(4): 355-9.
Litvan, I., K. P. Bhatia, et al. (2003). "Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders." Mov Disord **18**(5): 467-86.
Lohmann, E., S. Thobois, et al. (2009). "A multidisciplinary study of patients with early-onset PD with and without parkin mutations." Neurology **72**(2): 110-6.

Marder, K., G. Levy, et al. (2003). "Familial aggregation of early- and late-onset Parkinson's disease." Ann Neurol **54**(4): 507-13.
Marek, K., R. Innis, et al. (2001). "[123I]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression." Neurology **57**(11): 2089-94.
Martin, W. E., W. I. Young, et al. (1973). "Parkinson's disease. A genetic study." Brain **96**(3): 495-506.
Marttila, R. J. and U. K. Rinne (1977). "Disability and progression in Parkinson's disease." Acta Neurol Scand **56**(2): 159-69.
Mayeux, R., J. Denaro, et al. (1992). "A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender." Arch Neurol **49**(5): 492-7.
Mindham, R. H. (1970). "Psychiatric symptoms in Parkinsonism." J Neurol Neurosurg Psychiatry **33**(2): 188-91.
Mjones (1949). "Paralysis agitans: a clinical and genetic study." Acta Psychiatr Neurol Scand **25**(suppl 54): 1-195.
Montgomery, E. B., Jr., K. B. Baker, et al. (1999). "Abnormal performance on the PD test battery by asymptomatic first-degree relatives." Neurology **52**(4): 757-62.
Mori, H., T. Kondo, et al. (1998). "Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q." Neurology **51**(3): 890-2.
Morris, H. R. (2005). "Genetics of Parkinson's disease." Ann Med **37**(2): 86-96.
Morrish, P. K., J. S. Rakshi, et al. (1998). "Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET." J Neurol Neurosurg Psychiatry **64**(3): 314-9.
Muenter, M. D., L. S. Forno, et al. (1998). "Hereditary form of parkinsonism--dementia." Ann Neurol **43**(6): 768-81.
Mutch, W. J., I. Dingwall-Fordyce, et al. (1986). "Parkinson's disease in a Scottish city." Br Med J (Clin Res Ed) **292**(6519): 534-6.
Nath, U., R. Thomson, et al. (2005). "Population based mortality and quality of death certification in progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)." J Neurol Neurosurg Psychiatry **76**(4): 498-502.
Nausieda, P. A. (1992). Sleep in Parkinson's Disease. New York, Marcel Dekker Inc.
Nilsson, F. M., L. V. Kessing, et al. (2001). "Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study." Acta Psychiatr Scand **104**(5): 380-6.
Nilsson, F. M., L. V. Kessing, et al. (2002). "Major depressive disorder in Parkinson's disease: a register-based study." Acta Psychiatr Scand **106**(3): 202-11.
O'Sullivan, S. S., D. R. Williams, et al. (2008). "Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study." Mov Disord **23**(1): 101-6.
Oerlemans, W. G. and A. W. de Weerd (2002). "The prevalence of sleep disorders in patients with Parkinson's disease. A self-reported, community-based survey." Sleep Med **3**(2): 147-9.
Olson, E. J., B. F. Boeve, et al. (2000). "Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases." Brain **123 (Pt 2)**: 331-9.
Pantelatos, A. and F. Fornadi (1993). "Clinical features and medical treatment of Parkinson's disease in patient groups selected in accordance with age at onset." Adv Neurol **60**: 690-7.

Paulus, W. and K. Jellinger (1991). "The neuropathologic basis of different clinical subgroups of Parkinson's disease." J Neuropathol Exp Neurol **50**(6): 743-55.
Paviour, D. C., R. A. Surtees, et al. (2004). "Diagnostic considerations in juvenile parkinsonism." Mov Disord **19**(2): 123-35.
Payami, H., S. Zareparsi, et al. (2002). "Familial aggregation of Parkinson disease: a comparative study of early-onset and late-onset disease." Arch Neurol **59**(5): 848-50.
Pederzoli, M., F. Girotti, et al. (1983). "L-dopa long-term treatment in Parkinson's disease: age-related side effects." Neurology **33**(11): 1518-22.
Peppas, G., V. G. Alexiou, et al. (2008). "Epidemiology of constipation in Europe and Oceania: a systematic review." BMC Gastroenterol **8**: 5.
Peto, V., C. Jenkinson, et al. (1995). "The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease." Qual Life Res **4**(3): 241-8.
Poewe, W. (2008). "Non-motor symptoms in Parkinson's disease." Eur J Neurol **15 Suppl 1**: 14-20.
Pollock, M. and R. W. Hornabrook (1966). "The prevalence, natural history and dementia of Parkinson's disease." Brain **89**(3): 429-48.
Ponsen, M. M., D. Stoffers, et al. (2004). "Idiopathic hyposmia as a preclinical sign of Parkinson's disease." Ann Neurol **56**(2): 173-81.
Porter, B., R. Macfarlane, et al. (2006). "The prevalence of Parkinson's disease in an area of North Tyneside in the North-East of England." Neuroepidemiology **26**(3): 156-61.
Portin, R. and U. K. Rinne (1987). "Predictive factors for cognitive deterioration and dementia in Parkinson's disease." Adv Neurol **45**: 413-6.
Portman, A. T., N. Giladi, et al. (2001). "The nigrostriatal dopaminergic system in familial early onset parkinsonism with parkin mutations." Neurology **56**(12): 1759-62.
Pramstaller, P. P., M. G. Schlossmacher, et al. (2005). "Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers." Ann Neurol **58**(3): 411-22.
Quinn, N., P. Critchley, et al. (1987). "Young onset Parkinson's disease." Mov Disord **2**(2): 73-91.
Ramirez, A., A. Heimbach, et al. (2006). "Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase." Nat Genet **38**(10): 1184-91.
Reid, W. G., G. A. Broe, et al. (1989). "The neuropsychology of de novo patients with idiopathic Parkinson's disease: the effects of age of onset." Int J Neurosci **48**(3-4): 205-17.
Remy, P., M. Doder, et al. (2005). "Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system." Brain **128**(Pt 6): 1314-22.
Rippon, G. A. and K. S. Marder (2005). "Dementia in Parkinson's disease." Adv Neurol **96**: 95-113.
Robins, A. H. (1976). "Depression in patients with Parkinsonism." Br J Psychiatry **128**: 141-5.
Rocca, W. A., J. H. Bower, et al. (2001). "Time trends in the incidence of parkinsonism in Olmsted County, Minnesota." Neurology **57**(3): 462-7.
Rocca, W. A., S. K. McDonnell, et al. (2004). "Familial aggregation of Parkinson's disease: The Mayo Clinic family study." Ann Neurol **56**(4): 495-502.

Ross, G. W., R. D. Abbott, et al. (2006). "Association of olfactory dysfunction with incidental Lewy bodies." Mov Disord **21**(12): 2062-7.
Ross, G. W., H. Petrovitch, et al. (2008). "Association of olfactory dysfunction with risk for future Parkinson's disease." Ann Neurol **63**(2): 167-73.
Royal College of Physicians (2006). National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. London.
Santamaria, J., E. Tolosa, et al. (1986). "Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism." Neurology **36**(8): 1130-3.
Sasaki, S., A. Shirata, et al. (2004). "Parkin-positive autosomal recessive juvenile Parkinsonism with alpha-synuclein-positive inclusions." Neurology **63**(4): 678-82.
Schenck, C. H., S. R. Bundlie, et al. (1996). "Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder." Neurology **46**(2): 388-93.
Scherfler, C., N. L. Khan, et al. (2004). "Striatal and cortical pre- and postsynaptic dopaminergic dysfunction in sporadic parkin-linked parkinsonism." Brain **127**(Pt 6): 1332-42.
Schrag A, B.-S. Y., Quinn NP. (2000). "Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London." Br Med J **321**(7252): 21-2.
Schrag, A., Y. Ben-Shlomo, et al. (2002). "How valid is the clinical diagnosis of Parkinson's disease in the community?" J Neurol Neurosurg Psychiatry **73**(5): 529-34.
Schrag, A., Y. Ben-Shlomo, et al. (1999). "Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study." Lancet **354**(9192): 1771-5.
Schrag, A., Y. Ben-Shlomo, et al. (2000). "Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London." Bmj **321**(7252): 21-2.
Schrag, A. and N. Quinn (2000). "Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study." Brain **123 (Pt 11)**: 2297-305.
Schuurman, A. G., M. van den Akker, et al. (2002). "Increased risk of Parkinson's disease after depression: a retrospective cohort study." Neurology **58**(10): 1501-4.
Schwab, R. S., A. C. England, et al. (1959). "Akinesia in Parkinson's disease." Neurology **9**(1): 65-72.
Shiba, M., J. H. Bower, et al. (2000). "Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study." Mov Disord **15**(4): 669-77.
Shih, M. C., L. A. Franco de Andrade, et al. (2007). "Higher nigrostriatal dopamine neuron loss in early than late onset Parkinson's disease?--a [99mTc]-TRODAT-1 SPECT study." Mov Disord **22**(6): 863-6.
Slaughter, J. R., K. A. Slaughter, et al. (2001). "Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease." J Neuropsychiatry Clin Neurosci **13**(2): 187-96.
Sommer, U., T. Hummel, et al. (2004). "Detection of presymptomatic Parkinson's disease: combining smell tests, transcranial sonography, and SPECT." Mov Disord **19**(10): 1196-202.
Stern, Y., K. Marder, et al. (1993). "Antecedent clinical features associated with dementia in Parkinson's disease." Neurology **43**(9): 1690-2.
Stocchi, F., L. Vacca, et al. (2001). "Sleep disorders in Parkinson's disease." Adv Neurol **86**: 289-93.

Sutcliffe, R. L. and J. R. Meara (1995). "Parkinson's disease epidemiology in the Northampton District, England, 1992." Acta Neurol Scand **92**(6): 443-50.
Sutcliffe, R. L., R. Prior, et al. (1985). "Parkinson's disease in the district of the Northampton Health Authority, United Kingdom. A study of prevalence and disability." Acta Neurol Scand **72**(4): 363-79.
Sveinbjornsdottir, S., A. A. Hicks, et al. (2000). "Familial aggregation of Parkinson's disease in Iceland." N Engl J Med **343**(24): 1765-70.
Tandberg, E., J. P. Larsen, et al. (1996). "The occurrence of depression in Parkinson's disease. A community-based study." Arch Neurol **53**(2): 175-9.
Tandberg, E., J. P. Larsen, et al. (1998). "A community-based study of sleep disorders in patients with Parkinson's disease." Mov Disord **13**(6): 895-9.
Tanner CM, K. I., Goertz CG, Carvey PM, Klawans HL. (1985). "Clinical course in Parkinson's disease: relationship to age at onset." J Neurol **232**(suppl): 25.
Tanner, C. M. and J. W. Langston (1990). "Do environmental toxins cause Parkinson's disease? A critical review." Neurology **40**(10 Suppl 3): suppl 17-30; discussion 30-1.
Tanner, C. M., R. Ottman, et al. (1999). "Parkinson disease in twins: an etiologic study." Jama **281**(4): 341-6.
Taylor, K. S., C. E. Counsell, et al. (2006). "Pilot study of the incidence and prognosis of degenerative Parkinsonian disorders in Aberdeen, United Kingdom: methods and preliminary results." Mov Disord **21**(7): 976-82.
Teravainen, H., L. Forgach, et al. (1986). "The age of onset of Parkinson's disease: etiological implications." Can J Neurol Sci **13**(4): 317-9.
Thobois, S., M. J. Ribeiro, et al. (2003). "Young-onset Parkinson disease with and without parkin gene mutations: a fluorodopa F 18 positron emission tomography study." Arch Neurol **60**(5): 713-8.
Tilling, K., J. A. Sterne, et al. (2001). "Estimation of the incidence of stroke using a capture-recapture model including covariates." Int J Epidemiol **30**(6): 1351-9; discussion 1359-60.
Twelves, D., K. S. Perkins, et al. (2003). "Systematic review of incidence studies of Parkinson's disease." Mov Disord **18**(1): 19-31.
Ueki, A. and M. Otsuka (2004). "Life style risks of Parkinson's disease: association between decreased water intake and constipation." J Neurol **251 Suppl 7**: vII18-23.
van de Warrenburg, B. P., M. Lammens, et al. (2001). "Clinical and pathologic abnormalities in a family with parkinsonism and parkin gene mutations." Neurology **56**(4): 555-7.
Van Den Eeden, S. K., C. M. Tanner, et al. (2003). "Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity." Am J Epidemiol **157**(11): 1015-22.
Walsh, K. and G. Bennett (2001). "Parkinson's disease and anxiety." Postgrad Med J **77**(904): 89-93.
Ward C, G. W. (1990). Research diagnostic criteria for Parkinson's disease. New York, Raven Press.
Ware, J. E., Jr. and C. D. Sherbourne (1992). "The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection." Med Care **30**(6): 473-83.
Weisskopf, M. G., H. Chen, et al. (2003). "Prospective study of phobic anxiety and risk of Parkinson's disease." Mov Disord **18**(6): 646-51.

Williams, D. R., J. D. Warren, et al. (2008). "Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism." J Neurol Neurosurg Psychiatry **79**(6): 652-5.
Wirdefeldt, K., M. Gatz, et al. (2004). "No evidence for heritability of Parkinson disease in Swedish twins." Neurology **63**(2): 305-11.
Wooten, G. F., L. J. Currie, et al. (2004). "Are men at greater risk for Parkinson's disease than women?" J Neurol Neurosurg Psychiatry **75**(4): 637-9.
Yamamura, Y. (1998). "Clinical, pathologic and genetic studies on autosomal recessive early-onset parkinsonism with diurnal fluctuation." Parkinsonism Relat Disord **4**: 65-72.
Yamamura, Y., I. Sobue, et al. (1973). "Paralysis agitans of early onset with marked diurnal fluctuation of symptoms." Neurology **23**(3): 239-44.
Yokochi, M. (1997). "Familial juvenile parkinsonism." Eur Neurol **38 Suppl 1**: 29-33.
Yokochi, M., H. Narabayashi, et al. (1984). "Juvenile parkinsonism--some clinical, pharmacological, and neuropathological aspects." Adv Neurol **40**: 407-13.
Yokochi M, N. H. (1981). Clinical characteristics of juvenille parkinsonism. Tumbridge Wells, Pitman medical.
Zetusky, W. J., J. Jankovic, et al. (1985). "The heterogeneity of Parkinson's disease: clinical and prognostic implications." Neurology **35**(4): 522-6.
Ziemssen, T. and H. Reichmann (2007). "Non-motor dysfunction in Parkinson's disease." Parkinsonism Relat Disord **13**(6): 323-32.

Appendices

Additional Tables

Appendix Table 1: Table of GP Study Codes

Unitary Authority	*Number of practices*	*Total number of practices within group*	*GP Study Code range available*
Cardiff	54	54	101-154
Vale of Glamorgan Rhondda Cynon Taff Bridgend	19 43 19	81	201-281
Newport	22	22	301-322
Caerphilly Torfaen Blaenau Gwent Monmouthshire	31 13 19 14	77	401-477
Methyr Tydfil	13	13	501-513
Neath Port Talbot Swansea	23 36	59	601-659
Carmarthenshire Pembrokeshire Ceredigion	26 18 27	60	701-760
Powys Wrexham Gwenydd	17 23 27	67	801-867
Conwy Denbighshire Flintshire Anglessey	19 17 25 11	72	901-972
Outside Wales	unlimited	unlimited	999

Appendix Table 2 : Search terms used for final search strategy

I) Diagnostic Codes

Search Term	Read Code
Parkinson's disease	F 12
Parkinson's disease and subgroups	F 12 – F 12 z
Paralysis Agitans	F 120
Parkinsonism secondary to drugs	F 121
Malignant Neuroleptic Syndrome	F 122
Post encephalitic parkinsonism	F 123
Parkinsonism secondary to external agents	F 12 w
Secondary parkinsonism unspecified	F 12 x
Parkinson's disease not otherwise specified	F 12 z

II) Tremor Symptoms

Search Term	Read Code
Tremor not otherwise specified	RO 103
Tremor symptom	IB 22
On examination, fine tremor	2975
On examination, coarse tremor	2976
On examination, intention tremor	2977
On examination, Parkinsonian tremor	2974
Senile tremor	R 20
Essential and other specified form of tremor	F 131

III) Medication

Search Term	Read Code
Dopaminergic drugs	dq...
Anticholinergics	dv...

Appendix Table 3 : Diagnostic Read Codes 5-byte version 2 used to generate list 1

Diagnosis	Read Code
Parkinson's disease	F12
Parkinson's disease and below	F12 – F12z
- Paralysis agitans	F120
- Parkinsonism 2ry to drugs	F121
- Malignant neuroleptic syndrome	F122
- Post encephalitic parkinsonism	F123
- 2ry parkinsonism due to other external agents	F12w
- 2ry parkinsonism, unspecified	F12x
- Parkinson's disease, NOS	F12z

Appendix Table 4 : Drugs Read Codes 5-byte version 2 used to generate list 2 (otherwise Drug group CNS Drugs – parkinsonism- dopaminergic drugs excluding amantadine (dq4..) and bromocriptine (dq5..))

Drug name	Read Code
Levodopa	dq1..
Levodopa with benserazide / Co-beneldopa / Madopar	dq2..
Levodopa with carbidopa/ Co-careldopa / Sinemet	dq3..
Selegiline	dq6..
Lisuride maleate	dq7..
Pergolide mesylate	dq8..
Apomorphine hydrochloride	dq9..
Ropinirole hydrochloride	dqA..
Cabergoline	dqB..
Tolcapone	dqC..
Entacapone	dqD..
Pramipexole	dqE..

Publications

The effect of onset age on the clinical features of Parkinson's disease
M. M. Wickremaratchi, Y. Ben-Shlomo and H. R. Morris
European Journal of Neurology 2009

Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis
M M Wickremaratchi, D Perera, C O'Loghlen, D Sastry, E Morgan, A Jones, P Edwards, N P Robertson, C Butler, H R Morris, Y Ben-Shlomo
Journal of Neurology, Neurosurgery and Psychiatry 2009

Published Abstracts

Wickremaratchi, M. M., Y. Ben-Shlomo, et al. (2009). "Distinct motor features of young onset Parkinson's disease - A community based case control study." Movement Disorders **24**: S133-S133.

Wickremaratchi, M. M., Y. Ben-Shlomo, et al. (2008). "Non motor features in young onset Parkinson's disease." Movement Disorders **23**(1): S245-S245.

Wickremaratchi, M. M., E. Morgan, et al. (2007). "Community based prevalence study of Parkinson's disease describing age at onset distribution in Cardiff, UK." Movement Disorders **22**: S243-S243.

Wickremaratchi, M. M., A. Jones, et al. (2006). "A population based study of young onset Parkinson's disease in South Wales." Journal of Neurology Neurosurgery and Psychiatry **77**(1): 129-129.

Project Paperwork

BSQ (Basic screening questionnaire)

Clinic Consent Forms

Clinic assessment proformas

LHQ (Life History Questionnaire, includes Epworth Sleepiness Score)

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ID:

Screening Movement Disorders Questionnaire

Section A : Personal Details

[1]Name: .....

[2]Address: .....

.....

[3]Postcode : .....

[4]Tel no : .....

[5]Mobile no : .....

[8]Date of Birth: .....

[9]Place of Birth: .....

[6]GP name: .....

[7]GP address: .....

.....

Best day/ time to ring:

.....

[10]Gender : [1]M / [2]F

[11]Hospital Consultant (for PD/tremor/movement problem if applicable, otherwise leave blank): .....

[12]Hospital (for PD/tremor/movement problem): .....

Section B : Consent

Please read and initial the boxes if you agree:-

Initials

- [1]I give permission for my medical records to be looked at confidentially by members of the research team who would not normally be involved in my medical care. ☐
- [2]I agree that my GP and hospital consultant can be informed of my participation in this study ☐
- [3]I agree that my clinical details can be stored in a secure research database on the NHS hospital computer network. (You may ask for your personal information to be removed from this database at any time, in accordance with the Data Protection Act 1998). ☐
- [4]I would be willing to take part in the research project:

Please circle

  - [a]by filling in questionnaires about my condition [1]Yes [2]No
  - [b]by filling in questionnaires and attending a specialist clinical assessment [1]Yes [2]No

- [5]I do not have Parkinson's disease ☐

Signed : ..... Date : .....

Name (please print) : .....

ID:

Section C : Questionnaire

This questionnaire asks some questions about your symptoms, how they started and what treatment you have had. **Some of the questions may not be relevant to you or your illness.** We would be grateful if you could answer each question and answer no/don't know if needed.

If you have any difficulty with the questions please call the research team on 02920 743454/745821 or e-mail Dr Mirdhu Wickremaratchi on wpmmmw@cf.ac.uk

	Symptom	Q1. YES	Q1. NO	Q2. FIRST SYMPTOM (tick one box only)
1. Which of these **symptoms have/ do** you experience as part of your PD, tremor or difficulty with movement? **(please tick all boxes that apply)** 2. Of these, which was the very **first**? **(please only tick one symptom. If you had more than one symptom at onset, tick the one that was most severe)**	(a) Tremor/shakiness of limb when relaxing or at rest	1☐	2☐	1☐
	(b) Stiffness/rigidity of limb	1☐	2☐	2☐
	(c) Slowness	1☐	2☐	3☐
	(d) Walking difficulties	1☐	2☐	4☐
	(e) Handwriting problems	1☐	2☐	5☐
	(f) Frozen shoulder	1☐	2☐	6☐
	(g) Stooped posture	1☐	2☐	7☐
	(h) Reduced arm swing	1☐	2☐	8☐
	(i) Difficulty turning in bed	1☐	2☐	9☐
	(j) Other symptom	1☐	2☐	10☐

If other symptom (please specify)
.....

3. **When** did you notice the **first** symptom? e.g. Oct 2004 or Autumn 2004	a) Month: ..... b) Season:..... c) Year: .....
4. **Who** first diagnosed you with having PD, tremor or a movement disorder?	Doctor's name :..... Specialty: 1GP☐, 2Neurologist☐, 3Geriatrician☐, 4Other☐
5. What month and year was your diagnosis made?	(a) Month ..... (b) Year.....
How long after your first symptom was the diagnosis made? **(indicate either in months or years)**	(c) Months..... (d) Years .....
What was the diagnosis?	(e) .....

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	[1]Yes	[2]No	[3]Don't know
6a) Did your symptoms **start** on **one side** first?	☐	☐	☐
6b) Do your symptoms remain **worse** on that side more than the other?	☐	☐	☐
7. Have your symptoms worsened since they started?	☐	☐	☐
8. Did you have the following **within 2 years** of your first symptom :	[1]Yes	[2]No	[3]Don't know
a) More than 2 falls per year not related to freezing up	☐	☐	☐
b) Urinary incontinence / retention	☐	☐	☐
c) Memory problems severe enough to affect your everyday life	☐	☐	☐
9. Have you taken **L dopa** containing medications sinemet, madopar, co-careldopa, co-beneldopa, stalevo	☐	☐	☐
10a) If yes, did you have a **good** response to this medication within the first 12 months of taking it? (good = 70 % improvement or better)	☐	☐	☐
10b) Has this **good** response been maintained for 5 years since starting? (if you have taken it for less than 5 yrs, have you had a good response ever since you started)	☐	☐	☐
11. Have you developed any **problems** with either involuntary movements or fidgeting (dyskinesias) related to medication, or wearing off of your medication before the next dose is due or at other times (on/off fluctuations) ?	☐	☐	☐

12) Around the time your symptoms **started**, were you taking any of the following?

	[1]Yes	[2]No	[3]Don't Know	13. Name of drug
12 a) Anti-sickness medication?	☐	☐	☐	
12 b) Anti-dizziness medication?	☐	☐	☐	
12 c) Antidepressants?	☐	☐	☐	
12 d) Any medication for a psychiatric condition?	☐	☐	☐	

14. Details of any other medication taken around the time your symptoms first started:

15. Details of any other events around the time your symptoms first started e.g. operations, head injuries, major infections?

Thank you for taking the time to fill out this questionnaire.

ID: Date:

Department of Neurology, Ophthalmology and Audiological Medicine
Head of Department Professor C M Wiles BSc PhD FRCP

Uned Niwroleg ac Offthalmoleg Awdiolegol Meddygaeth
Pennaeth Uned Yr Athro C M Wiles BSc PhD FRCP

CARDIFF UNIVERSITY
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COMPARATIVE STUDY OF EARLY AND LATER ONSET PARKINSON'S ISEASE WITHIN THE GENERAL POPULATION

ATIENT CONSENT FORM

	initials
I have read the attached information sheet on the above project and been ven a copy to keep. I have had the opportunity to ask questions about the project and nderstand why the research is being done and any foreseeable risks involved. **know how to contact the research team if I need to.**	☐
I agree to give a sample of blood for research in the above project. I understand w the sample will be collected, that giving a sample for this research is voluntary d that I am free to withdraw my approval for the use of the sample at any time without ving a reason and without my medical treatment or my legal rights being affected. This mple will be used to study inherited material (DNA) and the chemical make-up of the ood (Plasma/Serum).	☐
I give permission for my medical records to be looked at confidentially by members the medical research team who would not normally be involved with my clinical care.	☐
I give permission for a videotape examination, in which I am personally entifiable, to be stored as part of my clinical record and to be used for teaching rposes, shown to doctors and health care workers.	☐
	YES ☐ NO ☐
I would like to be informed of research results that might indicate that a test for my ndition could be developed which might be of use to me or my family.	
I understand that I will not benefit financially if this research leads to the evelopment of new treatments or new tests.	☐
I agree that the DNA, plasma, that I have given can e looked after and stored for use in future projects, as described in the information eet. I understand that this research may be carried out by individuals other than the iginal researchers and that this may include commercial companies.	☐
I agree that my own doctor (GP and/or hospital) can be informed of clinical ssessment, which takes place as part of this study and that this can form part of my edical records.	☐
I agree that my clinical details can be stored in a clinical research database the NHS hospital computer network and understand that a separate anonymised search database will be used to store research results. I understand that I may ask for y personal information to be removed from this database at any time, in accordance with e Data Protection Act 1998.	☐

ID: Date:

I understand that information held by the NHS and records maintained by the General gistry Office may be used to keep in touch with me and follow up my health status. ☐

I am happy to receive information on future research projects, by telephone or letter, nout any commitment to participation ☐

Name of Subject	Date	Signature
Name of person giving assent if subject unable	Date	Signature
Name of researcher	Date	Signature

Thank you for your participation in this study.

ID:

Date:

Department of Neurology, Ophthalmology and Audiological Medicine
Head of Department Professor C M Wiles BSc PhD FRCP

Uned Niwroleg ac Offthalmoleg Awdiolegol Meddygaeth
Pennaeth Uned Yr Athro C M Wiles BSc PhD FRCP

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

DNA AND CELL LINE REPOSITORY INFORMED CONSENT FORM

I hereby consent to the **collection of blood for submission to the European Collection of Cell Cultures (ECACC)**, a British based research resource.

I understand that the repositories **collect, stores, and distribute cell cultures and DNA samples from people** with many kinds of disorders, from unaffected family members, and from other healthy people and that the purpose of this collection is to make specimens available for use in research, teaching, therapeutics and diagnostic purposes to responsible investigators in the UK and around the world.

I understand that the ECACC will take measures to protect my privacy, and that my blood or tissue specimen will be given a code number, and my name will not be submitted to the ECACC. **Some patient identification, such as age, sex, diagnosis, and race, will be made available to the Repository and scientists.**

I understand that there will be no direct benefit or payment to me for participating, but my sample may benefit the community at large or some particular group. Because researchers will not have access to my identity, it will not be possible to provide me or my physician with the eventual results of studies that might be performed using my ECACC specimen. My sample will stay in the Repository indefinitely and I will not be able to withdraw it. If I have any questions or complications relating to collection of this specimen, I should contact Dr Huw Morris or a member of his team on 02920 743798, who collected the specimen.

Name of subject	Date	Signature
Name of researcher	Date	Signature

ID: Date:

Appendix 2

Consent form for use when staff other than medical photographers are making photographic/video recordings of patients.

Cardiff and Vale NHS Trust/University of Wales College of Medicine (UWCM)
Photography/Video Recording of Patients

Cardiff and Vale NHS Trust/UWCM has adopted a policy to give you the right to control the future use of photographs/video recordings taken of you during the course of your treatment. Please sign in the appropriate place(s) below, once the purpose of the photography/video recording has been explained to you.

Consent: PLEASE TICK AS APPROPRIATE

☐ I consent to photograph(s)/video recording(s) being taken for my personal medical case-notes only.

☐ I consent to photograph(s)/video recording(s) being taken for my personal medical case-notes and being used for teaching of medical, dental, nursing and healthcare staff and students in the UK and abroad.

The patient has the right to withdraw consent at any time by contacting the Media Resources Centre.

Name of Patient (PLEASE PRINT) _____

Signature _____

Hospital Number _____ DOB _____ Date _____

☐ In addition, I consent to my photograph(s)/video recording(s) being published in an open access journal, textbook or other form of medical publication (which may include the internet), and therefore may be seen by the general public as well as medical professionals.

I understand that once published, it will not be possible to completely withdraw this consent.

Name of Patient (PLEASE PRINT) _____

Signature _____

Hospital Number _____ DOB _____ Date _____

Full name and signature of medical practitioner requesting illustrations and obtaining consent.

Name (PLEASE PRINT) _____

Department NEUROLOGY _____

Position (IF OTHER THAN CONSULTANT) _____

Signature _____

Date _____

ID: Date:

Department of Neurology, Ophthalmology and Audiological Medicine
Head of Department Professor C M Wiles BSc PhD FRCP

Uned Niwroleg ac Offthalmoleg Awdiolegol Meddygaeth
Pennaeth Uned Yr Athro C M Wiles BSc PhD FRCP

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

A COMPARATIVE STUDY OF EARLY AND LATER ONSET PARKINSON'S DISEASE WITHIN THE GENERAL POPULATION

DNA AND CELL LINE REPOSITORY INFORMED CONSENT FORM
(taken from **NINDS HUMAN GENETICS RESOURCE CENTER)**

I hereby consent to the **collection of blood for submission to the NINDS Human Genetics Resource Center**: DNA and Cell Line Repository at the Coriell Cell Repositories, a research resource supported by the Institute of Neurological Disorders and Stroke.

I understand that the repositories **collect, stores, and distribute cell cultures and DNA samples from people** with many kinds of disorders, from unaffected family members, and from other healthy people and that the purpose of this collection is to make specimens available for use in research, teaching and industry. I understand that the sample could be used to study any type of disease and not just Parkinson's. I understand that samples collected will be used to study genes and that the blood will be used for the preparation of DNA and possibly, an immortalised cell line.

I understand that the NINDS Repository will take measures to protect my privacy, and that my blood or tissue specimen will be given a code number and my name will not be submitted to the Coriell Cell Repositories, which is in accordance with HIPPA regulations. I also understand that the clinical and genetic data will be housed anonymously in a public database. **Some patient identification, such as age, sex, diagnosis, and race, will be made available to the Repository and scientists.**

I understand that this project has obtained a **Confidentiality Certificate from the Federal Government to help ensure privacy**. This Certificate means that the researchers/submitters cannot be forced to tell people who are not connected with the study about my participation, without my written consent. However, if there is threatened serious harm to myself or to others, it would be discussed with me, if possible, and disclosures would be made, if necessary, to protect me and other persons.

I understand that there will be no direct benefit or payment to me for participating, but my sample may benefit the community at large or some particular group. Because researchers will not have access to my identity, it will not be possible to provide me or my physician with the eventual results of studies that might be performed using my NINDS specimen. My sample will stay in the Repository indefinitely and I will have the option to withdraw at a later date, however I understand that it might not be entirely possible because of distribution and de-identification of samples and data. If I have any questions or complications relating to collection of this specimen, I should contact Dr Huw Morris or a member of his team on 02920 743798, who collected the specimen. If I have any questions about the Repository, I should contact Dr. Roderick Corrirear, Coriell Institute for Medical Research, 403 Haddon Avenue, Camden, New Jersey 08103. (Telephone: 00-1-856-757-9727).

Name of subject	Date	Signature
Name of researcher	Date	Signature

A Comparative Study of Early and Later Onset Parkinson's Disease

ID:	Clinic Date:

CONSENT CHECKLIST

	Discussed By:
Information sheet	
Chance to ask questions	
Research project consent	
NINDS consent	
Video consent	
Brain bank form	
Consent to access medical notes	
Consent to inform GP/ consultant	
Database (NHS + University)	
ONS database	
Interest in further studies/ consent to be contacted again	

ID:	Clinic Date:

DoB :	Initials :

Clinic Assessment: Doctor Administered

ID:	Clinic Date:

Clinical History and Examination

0a Referral Source

1 = GP search
2 = WPG database
3 = 2ry care – Neuro
4 = 2ry care – Geri
5 = 2ry care – PDNS
6 = 2ry care - other
7 = self ref - pamphlet
8 = self ref – PDS meeting
9 = other .....

0b Handedness

1 = Right 2 = Left

Clinical History

1. Onset

(a) 1st PD symptom	1 = tremor 6 = frozen shoulder 2 = slowness 7 = handwriting 3 = stiffness/rigidity 8 = turning in bed 4 = balance 9= manual dexterity 5 = walking	Date of onset	(b) Month..... (c) Year.....
(d) First contact with medical practitioner	1 = GP 2 = Hospital (e) Name _____	Date first sought medical advice	(f) Month..... (g)Year.....
(h) Who diagnosed PD	1 = GP 2 = Hospital (i) Name _____	Date of diagnosis	(j) Month..... (k) Year.....
(l) Progression	1 = Yes 2 = No		
(m) Symmetry of onset	1 = asymmetric 2 = bilateral/ symmetric		
(n) Side of onset	1 = Right 2 = Left		

ID:	Clinic Date:

2. Non-motor symptoms

		(1) Prodromal			Duration before motor symptoms (months) (not entered)	(2) Current	
		1=Yes	2=No	3=D/K		1=Yes	2=No
(a)	Constipation						
(b)	Depression						
(c)	Fatigue						
(d)	Sleep disturbance						
(e)	Loss of smell						
(f)	Parasthesia						
(g)	Other.....						

Further details of history (free hand):

ID:	Clinic Date:

3. Exclusion Criteria

	1=Y	2=N	**Details** (not entered)
(a) Dopamine blockers within 6 months of onset	☐	☐	
(b) Illicit drug use within 6 months of onset	☐	☐	
(c) Major head injury with LOC within 6 months of onset	☐	☐	
(d) Meningitis or Encephalitis within 6 months of onset	☐	☐	
(e) Sudden onset	☐	☐	
(f) Early cognitive disorder (significant impact on life within first 3 yrs or before onset)	☐	☐	
(g) Early bladder disturbance (urinary incontinence/ retention within 1st year)	☐	☐	
(h) Early postural instability/falls (within 1st year)	☐	☐	
(i) Early postural syncope (within 1st year)	☐	☐	

ID:	Clinic Date:

4. Dystonia : pre L dopa

Present	(a) At onset 1=Y☐ 2=N☐		(b) Prominent within first 2 years (if not at onset) 1=Y☐ 2=N☐		(c) Exercise induced 1=Y☐ 2=N☐		(d) Early morning 1=Y☐ 2=N☐	
Location if present	1=Y	2=N	1=Y	2=N	1=Y	2=N	1=Y	2=N
1) RUL	☐	☐	☐	☐	☐	☐	☐	☐
2) LUL	☐	☐	☐	☐	☐	☐	☐	☐
3) RLL	☐	☐	☐	☐	☐	☐	☐	☐
4) LLL	☐	☐	☐	☐	☐	☐	☐	☐
5) Neck	☐	☐	☐	☐	☐	☐	☐	☐
6) Oromandibular	☐	☐	☐	☐	☐	☐	☐	☐
7) Blepharospasm	☐	☐	☐	☐	☐	☐	☐	☐
8) Ocolugyric crisis	☐	☐	☐	☐	☐	☐	☐	☐
9) Axial	☐	☐	☐	☐	☐	☐	☐	☐
10) Other.....	☐	☐	☐	☐	☐	☐	☐	☐

5. Dystonia : L dopa related

Present	(a) Off period 1=Y☐ 2=N☐		(b) Peak dose 1=Y☐ 2=N☐		(c) Early morning 1=Y☐ 2=N☐		(d) Not dose-time related 1=Y☐ 2=N☐	
Location if present	1=Y	2=N	1=Y	2=N	1=Y	2=N	1=Y	2=N
1) RUL	☐	☐	☐	☐	☐	☐	☐	☐
2) LUL	☐	☐	☐	☐	☐	☐	☐	☐
3) RLL	☐	☐	☐	☐	☐	☐	☐	☐
4) LLL	☐	☐	☐	☐	☐	☐	☐	☐
5) Neck	☐	☐	☐	☐	☐	☐	☐	☐
6) Oromandibular	☐	☐	☐	☐	☐	☐	☐	☐
7) Blepharospasm	☐	☐	☐	☐	☐	☐	☐	☐
8) Ocolugyric crisis	☐	☐	☐	☐	☐	☐	☐	☐
9) Axial	☐	☐	☐	☐	☐	☐	☐	☐
10) Other.....	☐	☐	☐	☐	☐	☐	☐	☐

ID:	Clinic Date:

6. Hallucinations

	1=Y	2=N	
(a) Present	☐	☐	Start date: (b) Month ..... (c) Year.....
(d) Menacing	☐	☐	
(e) Insight retained	☐	☐	
(f) On medication when hallucinations occurred	☐	☐	
(g0) Hallucinations resolved with stopping/ reducing medication?	☐	☐	

		1=Y	2=N
(g) Which medication	(1)L dopa	☐	☐
	(2) Dopamine agonist	☐	☐
	(3) Anti-cholinergic	☐	☐
	(4) COMT inhibitor	☐	☐
	(5) NMDA	☐	☐
	(6) MAOB inhibitor	☐	☐
	(7) Other.....	☐	☐
(h) Type of hallucination	(1) Auditory	☐	☐
	(2) Visual	☐	☐
	(3) Olfactory	☐	☐
	(4) Tactile	☐	☐
	(5) Gustatory	☐	☐
(i) If auditory:	(1) Verbal	☐	☐
	(2) Musical	☐	☐
	(3) Other	☐	☐
(j) If verbal	(1) 1st person	☐	☐
	(2) 2nd person	☐	☐
	(3) 3rd person	☐	☐
(k) If visual	(1) Presence	☐	☐
	(2) Passage	☐	☐
	(3) Formed	☐	☐

ID:	Clinic Date:

7. Sleep disturbance

(a) Insomnia	1=Y☐	2=N☐
(b) Shout out/ kick out in sleep	1=Y☐	2=N☐
(c) Vivid dreams	1=Y☐	2=N☐
(d) Prominent nightmares	1=Y☐	2=N☐
(e) Sleep paralysis	1=Y☐	2=N☐
(f) Has your partner had to move to another bedroom because of your sleep problems	1=Y☐	2=N☐

8. Sleep benefit

(a) What is the best time of the day?	1 = immediately after you've woken 2 = mid morning 3 = lunchtime 4 = mid afternoon 5 = tea time 6 = evening	
(b) In general, how are you first thing in the morning?	1 = Cannot do much before medication ie off 2 = As good as with medication	
(c) Sleep benefit present	1 = no 2 = yes	
(d) If present, does this sleep benefit occur on a regular basis?	1 = no 2 = yes	(e) If so, what proportion of the time does it occur? 1 = <25% 2 = 26-50% 3 = 51-75% 4 = >75%
(f) If present have you had marked benefit from sleep within the first 3 years of onset?	1 = no 2 = yes	

ID:	Clinic Date:

9. Current PD Medication

(1) Drug name	Dose		(4) Freq	Times						(11) Start Date
	(2) Number	(3) Units*		(5)	(6)	(7)	(8)	(9)	(10)	
(a)										
(b)										
(c)										
(d)										
(e)										
(f)										
(g)										

* 1=micrograms/mcg, 2=milligrams/mg, 3=grams/g

10. Response to L Dopa

1 = Poor
2 = Moderate
3 = Good
4 = Excellent

ID:	Clinic Date:

11. Dyskinesias

(a) Are dyskinesias present		1=Y☐ 2=N☐
If present, when are they present?	(b) immediately after you've woken (c) mid morning (d) lunchtime (e) mid afternoon (f) tea time (g) evening	1=Y ☐ 2=N ☐ 1=Y ☐ 2=N ☐ 1=Y ☐ 2=N ☐ 1=Y ☐ 2=N ☐ 1=Y ☐ 2=N ☐ 1=Y ☐ 2=N ☐
(h) If present, when are they worse?	1 = just after you've woken 2 = mid morning 3 = lunchtime 4 = mid afternoon 5 = tea time 6 = evening	
When did they start?	(i) Month ..... (j)Year.....	
(k) What proportion of the waking day are dyskinesias present	0 = not present 1 = 1-25% 2 = 26-50% 3 = 51-75% 4 = 76-100%	32
(l) How disabling are they?	0 = not disabling 1 = mildly 2 = moderately 3 = severely 4 = completely	33
(m) How painful are they?	0 = not painful 1 = slightly 2 = moderately 3 = severely 4 = markedly	34

ID:	Clinic Date:

12. Early morning/ off period dystonia		
(a) Are off period dystonias present	0 = no 1 = yes	35
When did these start	(b) Month ..... (c)Year.....	
13. Motor fluctuations		
(a) Are motor fluctuations present	0 = no 1 = yes	
When did off periods start	(b) Month..... (c)Year.....	
(d) Are off periods predictable	0 = no 1 = yes	36
(e) Are off periods unpredictable	0 = no 1 = yes	37
(f) Do off periods come on suddenly within a few seconds	0 = no 1 = yes	38
(g) What proportion of the waking day is spent in an off state	0 = none 1 = 1-25% 2 = 26-50% 3 = 51-75% 4 = 76-100%	39
14. Others		
(a) Any anorexia, nausea or vomiting related to medication	0 = no 1 = yes	40
(b) Any sleep disturbance	0 = no 1 = yes	41

ID:	Clinic Date:

17. Freehand Family Tree

ID:	Clinic Date:

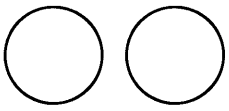
Clinical Examination

1. General

(a) Weight

	(1) seated	(2) supine	(3) standing	(4) Chair height to seat
(b) Height				
(c) Pulse				
(d) BP				

2. Eyes

		(1) Right	(2) Left	
		1 = normal 2 =abnormal	1= normal 2 = abnormal	
(a) Fundal Examination		☐ ☐	☐ ☐	
Pupils	(b) appearance	☐ ☐	☐ ☐	
	(c) light reaction	☐ ☐	☐ ☐	
(d) Visual fields (draw if abn) 		☐ ☐	☐ ☐	
(e) Visual acuity (PH)				
Eye movements	(f) Pursuit	(1) Horizontal 1=Normal 2= Abnormal	(2) Vertical 1=Normal 2=Abnormal	
	(g) Saccades	(1) Horizontal	(2) Upgaze	(3) Downgaze
	(i) Size	1=Normal 2= Abnormal	1=Normal 2= Abnormal	1=Normal 2= Abnormal
	(ii) Speed	1=Normal 2= Abnormal	1=Normal 2= Abnormal	1=Normal 2= Abnormal
(h) Supranuclear gaze palsy		1 = present 2 = absent		
(i) Nystagmus		0 = absent 1 = horizontal 2 = gaze evoked 3 = downbeat 4 = rotational		
Eye opening/ closing		(j) Apraxia 1 = present 2 = absent	(k) Blepharospasm 1 = present 2 = absent	

ID:	Clinic Date:

3. Other cranial nerves

(a) Facial power	☐ 1 = normal ☐ 2 = UMN facial ☐ 3 = LMN facial ☐ 4 = bifacial weakness	
(b) Ptosis	☐ 1 = absent ☐ 2 = present	
(c) Tongue movements	☐ 1 = normal ☐ 2 = spastic ☐ 3 = weak	
(d) Tongue appearance (wasting/ fasc)	☐ 1 = normal ☐ 2 = wasted ☐ 3 = fasciculation	
(e) Jaw jerk	☐ 1 = absent/ normal ☐ 2 = brisk	
(f) Facial jerks ☐1=absent ☐2=present	(g) Palmomental ☐1=absent ☐2=present	(h) Pout ☐1=absent ☐2=present
(i) Neck Flexion	☐ 1 = normal ☐ 2 = weak	
(j) Speech	0 = Normal 1 = Slight loss of expression/diction +/- volume 2 = Monotone, slurred but understandable. Mod impaired 3 = Marked impairment. Difficult to understand 4 = Unintelligible	18
(k) Facial expression	0 = Normal 1 = Minimal hypomimia, 2 = Slight but definite diminuation 3 = Moderate hypomimia, lips parted sometimes 4 = Masked/ fixed facies, complete loss of facial expression, lips parted ¼ inch or more	19

ID:	Clinic Date:

4. Tremor

(a) Tremor at rest	0 = Absent 1 = Slight and infrequent 2 = Mild + persistent/ moderate + infrequent 3 = Moderate and present most of the time 4 = Marked and present most of the time	20
		(1) Head/ face/lips
		(2) R UL
		(3) L UL
		(4) R LL
		(5) L LL
(b) Action/ Postural Tremor	0 = Absent 1 = Slight; present with action 2 = Moderate; present wit action 3 = Moderate ; posture holding and action 4 = Marked ; interferes with feeding	21
		(1) R
		(2) L

5. Rigidity

Limb rigidity	0 = Absent 1 = Slight or only on reactivation 2 = Mild to moderate 3 = Marked but with full ROM 4 = Severe, difficulty with full ROM	22
		(1) Neck
		(2) R UL
		(3) L UL
		(4) R LL
		(5) L LL

6. Bradykinesia

(a) Finger Taps	0 = Normal 1 = Mild slowing +/or reduction in amplitude 2 = Mod imp. Def early fatiguing . Occ arrests in movement 3 = Severely imp. Hesitation in initiation or frequent arrests 4 = Can barely perform the task	23
		(1) R
		(2) L
(b) Hand Movements	Open and close hands in rapid succession (score as above)	24
		(1) R
		(2) L
(c) Pronation - supination	Both hands simultaneously (score as above)	25
		(1) R
		(2) L
(d) Leg agility	Heel taps, picking up entire leg (score as above)	26
		(1) R
		(2) L

ID:	Clinic Date:

7. Posture and Gait		
(a) Arising from chair	0 = Normal 1 = Slow, may need more than one attempt 2 = Pushes self up from arms of seat 3 = Tends to fall back and may need more attempts 4 = Unable to rise without help	27
(b) Posture	0 = Normal erect 1 = Slightly stooped 2 = Moderately stooped 3 = Severely stooped with kyphosis 4 = Marked flexion with extreme abnormality of posture	28
(c) Gait	0 = Normal 1 = Slow, may shuffle, no festination/ propulsion 2 = With difficulty but requires no/ little assistance 3 = Severe gait disturbance requiring assistance 4 = Cannot walk at all even with assistance	29
(d) Postural stability	0 = Normal 1 = Retropulsion but recovers unaided 2 = Absence of postural response,would fall if not caught 3 = Very unstable, loses balance spontaneously 4 = Unable to stand without assistance	30
(e) Body Bradykinesia/ hypokinesia	0 = None 1 = Minimal slowness, deliberate 2 = Mild slowness + poverty of movement, maybe ↓ amp 3 = Moderate slowness, poverty or small amplitude 4 = Marked slowness, poverty or small amplitude	31

ID:	Clinic Date:

8. Power (MRC grade 0-5)			
		(1) Right	(2) Left
Upper limb	(a) Shoulder abduction		
	(b) Elbow extension		
	(c) Finger extension		
	(d) Finger abduction		
Lower limb	(e) Hip flexion		
	(f) Knee extension		
	(g) Ankle dorsiflexion		
	(h) Toe extension		

9. Reflexes (1 = normal, 2 =absent, 3 =reduced, 4 = pathologically brisk)			
		(1) Right	(2) Left
Upper limb	(a) Triceps		
	(b) Biceps		
	(c) Supinator		
Lower limb	(d) Knees		
	(e) Ankles		
(f) Plantars (1=normal, 2=upgoing, 3=mute)			

10. Sensation (1 =normal , 2 = abnormal)		
	(1) Right	(2) Left
a) Joint position sense		
b) Vibration sense		
c) Light touch		
d) Graphaesthesia		

11. Cerebellar signs (1=no, 2=yes)		
	(1) Right	(2) Left
a) Finger nose ataxia		
b) Intention tremor		
c) Dysdiodochokinesia		
d) Heel shin ataxia		
e) Ataxic gait		
f) Unable to tandem walk		

ID:	Clinic Date:

12. Final Diagnosis

a) Queens Square Brain Bank Criteria	☐ 1 = Yes ☐ 2 = No
b) MMW Final Diagnosis	
1) 1 = PSP 2 = MSA 3 = CBD 4 = Vascular Parkinsonism 5 = BET 6 = DIP 7 = Other	2) Other ....

ID:	Clinic Date:

Video Protocol v27/05/05

Video consent form

1. Face / trunk / hands – count backwards from 10 to 1.
2. Hands close up – count backwards from 10 to 1.
3. Face close up – count backwards from 10 to 1.
4. Eyes close up : open and close eyes x 5,

   : look up, down, left then right keeping head still.
5. Hands outstretched in front of face – 10 seconds.
6. Finger nose test : right x 3

   : left x 3
7. Finger taps, then each finger in turn : right – 10 seconds

   : left – 10 seconds.
8. Repeated hand grips, outstretched arms – 10 seconds.
9. Repeated pronation-supination, outstretched arms – 10 seconds.
10. Leg agility/ heel taps, lift heel 3 inches off the ground : right – 10 seconds

    : left – 10 seconds.
11. Full body view, arise from chair with arms folded across chest.
12. Walk in corridor : face on > 10 yards turn x 2.
13. Pull test, twice: first gentle tug on shoulders, second more forceful.
14. Reflexes.
15. Handwriting

ID:	Clinic Date:

DIAGNOSTIC CHECKLIST

	Diagnostic criteria	*Yes*	*No*
Mandatory	**Bradykinesia**		
+ 1 of :	Tremor		
	Rigidity		
	Postural instability		
Supportive :	Unilateral onset		
3 or more of :	Rest tremor		
	Progressive		
	Persistent asymmetry (side of onset worse)		
	Excellent response to L-dopa		
	Severe L-dopa induced chorea		
	l-dopa responsive for ≥ 5 yrs		
	Clinical course of ≥10 yrs		

Exclusion criteria	*Yes*	*No*
Repeated strokes and stepwise progression of PD symptoms		
Repeated head injury		
Encephalitis		
Oculogyric crisis		
Neuroleptic at onset		
Sustained remission		
Cerebellar signs		
Tumour/ hydrocephalus on CT head		
Negative response to large doses of L dopa		
MPTP exposure		
Relative exclusion criteria:		
Strictly unilateral features >3yrs		
Supranuclear gaze palsy		
Early severe autonomic involvement		
Early severe dementia		
Definite pyramidal signs		

Parkinson's Disease based on criteria	Yes	No

ID:	Clinic Date:

Handwriting for Video :

Copy this sentence in your normal handwriting **"Mary had a little lamb"** :

Copy Spiral :

Right :

Left :

Copy Spring :

Right

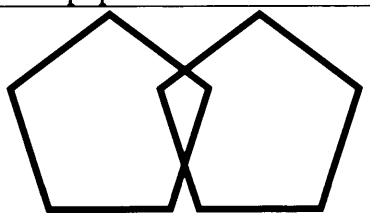
Left

ID:	Clinic Date:

Clinic Research Administrator Interview

ID: Clinic Date:

(A) Mini Mental State Examination

		Score (1 or 0)
1.	What day of the week is it ?	1
2.	What is the date today ?	2
3.	What is the month ?	3
4.	What is the season?	4
5.	What is the year ?	5
6.	Where are we now?	6
7.	What floor are we on?	7
8.	In which town are we?	8
9.	In which county/ district are we?	9
10.	In which country are we?	10
11-13	Repeat the following words : Lemon, Key, Ball (The examiner should pronounce the words at a rate of one per second. In case of difficulties, repeat up to 5 times.)	11 12 13
14-18	Subtract 7 from 100 and make 5 subtractions	14 15 16 17 18
19-21	Can you remember the 3 words from before?	19 20 21
22.	What is this? (show a pencil)	22
23.	What is this? (show a watch)	23
24.	Repeat the following " no ifs, and or buts"	24
25-27.	Follow a three-stage command : Take a piece of paper, fold it in half and put it on the floor"	25 26 27
28.	Read and obey what is written on this piece of paper ("Close your eyes")	28
29.	Write a sentence of your choice on this piece of paper.	29
30.	Copy this drawing on a piece of paper 	30
	Total	31

ID:	Clinic Date:

Close Your Eyes

Write a sentence :

ID: Clinic Date:

(B) Lang and Fahn Activities of Daily Living Dyskinesia Scale

SUBJECT	SCORE	DESCRIPTION
1. Handwriting or drawing	0	No dyskinesias are evident when you write, which is accomplished as well as your Parkinson's disease (PD) allows at the best of times (this may be small or partly legible).
	1	When dyskinesias are at their current maximum, writing is no different from the best performance without dyskinesias (writing may be small or illegible at the best of times but dyskinesias do not interfere with writing
	2	When dyskinesias are at their current maximum, they interfere with writing but allow you to complete the writing task successfully with only a slight increase in the time or effort required and no further increase in legibility compared with the best writing performance without dyskinesias
	3	When dyskinesias are at their current maximum, they cause substantial impairment in writing or drawing compared with the best performance without dyskinesias; result from the dyskinesias is more illegible than without dyskinesias and drawing shows more errors.
	4	When dyskinesias are at their current maximum, they make writing and drawing impossible. Because of dyskinesias, it is impossible to maintain contact between pen and paper long enough to write or draw (ie, it is impossible to produce even small, illegible script).
2. Cutting Food and Handling Utensils	0	No dyskinesias are evident when you feed yourself which is accomplished as well as your PD allows at the best times.
	1	When dyskinesias are at their current maximum, they do not interfere at all with cutting food and feeding yourself. The ability to feed yourself is no different from the best performance without dyskinesias (this includes slowness and clumsiness, possibly even requiring help at the best of times as a result of persistent problems with parkinsonism).
	2	When dyskinesias are at their current maximum, they definitely interfere with feeding but allow you to complete the necessary feeding task with only a slight increase in time or effort compared to the best performance without dyskinesias (any assistance required in cutting food or feeding relates mainly to the underlying parkinsonism and persists at the best of times without dyskinesias).
	3	When dyskinesias are at their current maximum, they cause substantial impairment in feeding compared with the best performance without dyskinesias; as a result of the dyskinesias, more help is required to cut food or feed yourself than at the best of times without dyskinesias
	4	When dyskinesias are at their current maximum, they make feeding impossible and even with full assistance from someone else, feeding is exceedingly difficult or impossible because of the presence of dyskinesias.

ID:	Clinic Date:

SUBJECT	SCORE	DESCRIPTION
3. Dressing	0	No dyskinesias are evident when you get dressed or undressed including outerwear to go outdoors that are as accomplished as well as your PD allows at the best of times.
	1	When dyskinesias are at their current maximum, they do not interfere at all with the performance of dressing tasks. These are completed no differently from the best performance without dyskinesias (this includes slowness and clumsiness possibly even requiring help at the best of times as a result of persistent problems with parkinsonism).
	2	When dyskinesias are at their current maximum, they definitely interfere with the performance of dressing tasks but allow you to complete them with only a slight increase in time or effort compared to the best performance without dyskinesias (any assistance required in getting dressed, including doing up buttons or getting arms into sleeves, related to the underlying parkinsonism and persists at the best of times without dyskinesias).
	3	When dyskinesias are at their current maximum, they cause substantial impairment in the performance of dressing tasks compared with the best performance without dyskinesias; as a result of the dyskinesias, more help is required for dressing than the best of times without dyskinesias.
	4	When dyskinesias are at their current maximum, they make performance of dressing tasks impossible and even with full assistance from someone else, dressing is exceedingly difficult or impossible because of the presence of dyskinesias.
4. Hygiene	0	No dyskinesias are evident when you wash, shower, bathe, shave, brush your teeth, and so on, that are accomplished as well as your PD allows at the best of times.
	1	When dyskinesias are at their current maximum, they do not interfere with the performance of hygiene tasks. These are completed no differently from the best performance without dyskinesias (this includes slowness and clumsiness possibly even requiring help at the best of times as a result of persistent problems with parkinsonism).
	2	When dyskinesias are at their current maximum, they definitely interfere with the performance of hygiene tasks but allow you to complete them with only a slight increase in time or effort compared to the best performance without dyskinesias (any assistance required in getting dressed, including doing up buttons or getting arms into sleeves, related to the underlying parkinsonism and persists at the best of times without dyskinesias).
	3	When dyskinesias are at their current maximum, they cause substantial impairment in the performance of hygiene tasks compared with the best performance without dyskinesias; as a result of the dyskinesias, more help is required for washing, grooming, and going to the bathroom than the best of times without dyskinesias.
	4	When dyskinesias are at their current maximum, they make performance of hygiene tasks impossible and even with full assistance from someone else, washing, grooming, and going to the bathroom are exceedingly difficult or impossible because of the presence of dyskinesias.

ID:	Clinic Date:

SUBJECT	SCORE	DESCRIPTION
5. Walking	0	No dyskinesias are evident when you walk which is accomplished as well as your PSD allows at the best of times.
	1	When dyskinesias are at their current maximum, they do not interfere at all with walking. The ability to walk is no different from your best walking without dyskinesias (this includes slowness, unsteadiness, freezing, and even the need for assistance at the best of times as a result of persistent problems with parkinsonism).
	2	When dyskinesias are at their current maximum, they definitely interfere with walking but still allow you to walk with only a slight increase in caution, time, or effort compared to the best performance without dyskinesias possibly as a result of more unsteadiness or more frequent stumbling (any assistance required for walking relates mainly to the underlying parkinsonism and persists at the best of times without dyskinesias).
	3	When dyskinesias are at their current maximum, they cause substantial impairment in walking compared with your best walking without dyskinesias; more help is required to walk than at the best of times without dyskinesias.
	4	When dyskinesias are at their current maximum, they make walking impossible and even with full assistance from someone else, ambulation is exceedingly difficult or impossible because of the presence of dyskinesias.

ID:	Clinic Date:

Clinic Assessment: Self Administered

ID:	Clinic Date:

BECK DEPRESSION INVENTORY

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2 or 3) next to the one statement in each group which **best** describes the way you have been feeling the **past week, including today**. If several such statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1	I do not feel sad.	0
	I feel sad.	1
	I am sad all the time and I can't snap out of it.	2
	I am so sad and unhappy that I can't stand it.	3
2	I am not particularly discouraged about the future.	0
	I feel discouraged about the future.	1
	I feel I have nothing to look forward to.	2
	I feel the future is hopeless and that things cannot improve.	3
3	I do not feel like a failure.	0
	I feel I have failed more than the average person.	1
	As I look back on my life, all I can see is a lot of failures.	2
	I feel I am a complete failure as a person.	3
4	I get as much satisfaction out of things as I used to.	0
	I don't enjoy things the way I used to.	1
	I don't get real satisfaction out of anything anymore.	2
	I am dissatisfied or bored with everything.	3
5	I don't feel particularly guilty.	0
	I feel guilty a good part of the time.	1
	I feel quite guilty most of the time.	2
	I feel guilty all of the time.	3

ID:	Clinic Date:

6	I don't feel I am being punished.	0
	I feel I may be punished.	1
	I expect to be punished.	2
	I feel I am being punished.	3
7	I don't feel disappointed in myself.	0
	I am disappointed in myself.	1
	I am disgusted with myself.	2
	I hate myself.	3
8	I don't feel I am any worse than anybody else.	0
	I am critical of myself for my weaknesses or mistakes.	1
	I blame myself all the time for my faults.	2
	I blame myself for everything bad that happens.	3
9	I don't have any thoughts of killing myself.	0
	I have thoughts of killing myself, but I would not carry them out.	1
	I would like to kill myself.	2
	I would kill myself if I had the chance.	3
10	I don't cry any more than usual.	0
	I cry more now than I used to.	1
	I cry all the time now.	2
	I used to be able to cry, but now I can't cry even though I want to.	3
11	I am no more irritated by things than I ever was.	0
	I am slightly more irritated now than usual.	1
	I am quite annoyed or irritated a good deal of the time.	2
	I feel irritated all the time.	3

ID:	Clinic Date:

12	I have not lost interest in other people.	0
	I am less interested in other people than I used to be.	1
	I have lost most of my interest in other people.	2
	I have lost all of my interest in other people.	3
13	I make decisions about as well as I ever could.	0
	I put off making decisions more than I used to.	1
	I have greater difficulty in making decisions more than I used to.	2
	I can't make decisions at all anymore.	3
14	I don't feel that I look any worse than I used to.	0
	I am worried that I am looking old or unattractive.	1
	I feel that there are permanent changes in my appearance that make me look unattractive.	2
	I believe that I look ugly.	3
15	I can work about as well as before.	0
	It takes an extra effort to get started at doing something.	1
	I have to push myself very hard to do anything.	2
	I can't do any work at all.	3
16	I can sleep as well as usual.	0
	I don't sleep as well as I used to.	1
	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.	2
	I wake up several hours earlier than I used to and cannot get back to sleep.	3
17	I don't get more tired than usual.	0
	I get tired more easily than I used to.	1
	I get tired from doing almost anything.	2
	I am too tired to do anything.	3

ID: Clinic Date:

18	My appetite is no worse than usual.	0
	My appetite is not as good as it used to be.	1
	My appetite is much worse now.	2
	I have no appetite at all anymore.	3
19	I haven't lost much weight, if any, lately.	0
	I have lost more than five pounds.	1
	I have lost more than ten pounds.	2
	I have lost more than fifteen pounds.	3
20	I am no more worried about my health than usual.	0
	I am worried about physical problems such as aches and pains, or upset stomach, or constipation.	1
	I am very worried about physical problems and it's hard to think of much else.	2
	I am so worried about my physical problems that I cannot think about anything else.	3
21	I have not noticed any recent change in my interest in sex.	0
	I am less interested in sex than I used to be.	1
	I have almost no interest in sex.	2
	I have lost interest in sex completely.	3

ID: Clinic Date:

PDQ-39 QUESTIONNAIRE

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
1. Had difficulty doing the leisure activities which you would like to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Had difficulty carrying bags of shopping?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Had problems walking half a mile?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Had problems walking 100 yards?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Had problems getting around the house as easily as you would like?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Had difficulty getting around in public?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Needed someone else to accompany you when you went out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Felt frightened or worried about falling over in public?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Been confined to the house more than you would like?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Had difficulty washing yourself?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Had difficulty dressing yourself?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Had problems doing up your shoe laces?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

*Please check that you have ticked **one box for each question** before going on to the next page.*

ID: Clinic Date:

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
14. Had problems writing clearly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Had difficulty cutting up your food?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Had difficulty holding a drink without spilling it?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Felt depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Felt isolated and lonely?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Felt weepy or tearful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Felt angry or bitter?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Felt anxious?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Felt worried about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23. Felt you had to conceal your Parkinson's from people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Avoided situations which involve eating or drinking in public?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Felt embarrassed in public due to having Parkinson's disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Felt worried by other people's reaction to you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Had problems with your close personal relationships?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner tick here*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29.Lacked support in the ways you need from your family or close friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

*Please check that you have ticked **one box for each question** before going on to the next page.*

ID:	Clinic Date:

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....

	Never	Occasionally	Sometimes	Often	Always
30. Unexpectedly fallen asleep during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Had problems with your concentration, e.g. when reading or watching TV?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Felt your memory was bad?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Had distressing dreams or hallucinations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Had difficulty with your speech?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Felt unable to communicate with people properly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Felt ignored by people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Had painful muscle cramps or spasms?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
38. Had aches and pains in your joints or body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
39. Felt unpleasantly hot or cold?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Please check that you have ticked ***one box for each question.***

Thank you for completing the PDQ 39 questionnaire

ID:	Clinic Date:

PATIENT DIARY

Please put an **X** in the correct box for every half-hour period, using the term that best describes your condition during the last few minutes of that half-hour. Only one X should be in each half-hour period. Please fill in every day for three days.

DAY 1

Date completed:

ıe (morning)	6.00	6.30	7.00	7.30	8.00	8.30	9.00	9.30	10.00	10.30	11.00	11.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
eep												

ıe (afternoon)	12.00	12.30	13.00	13.30	14.00	14.30	15.00	15.30	16.00	16.30	17.00	17.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
eep												

ıe (evening)	18.00	18.30	19.00	19.30	20.00	20.30	21.00	21.30	22.00	22.30	23.00	23.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
eep												

ıe (night)	24.00	24.30	01.00	01.30	02.00	02.30	03.00	03.30	04.00	04.30	05.00	05.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
eep												

ID:	Clinic Date:

PATIENT DIARY

Please put an **X** in the correct box for every half-hour period, using the term that best describes your condition during the last few minutes of that half-hour. Only one X should be in each half-hour period. Please fill in every day for three days.

DAY 2

Date completed:

ne (morning)	6.00	6.30	7.00	7.30	8.00	8.30	9.00	9.30	10.00	10.30	11.00	11.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
l off												
eep												

ne (afternoon)	12.00	12.30	13.00	13.30	14.00	14.30	15.00	15.30	16.00	16.30	17.00	17.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
l off												
eep												

ne (evening)	18.00	18.30	19.00	19.30	20.00	20.30	21.00	21.30	22.00	22.30	23.00	23.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
l off												
eep												

ne (night)	24.00	24.30	01.00	01.30	02.00	02.30	03.00	03.30	04.00	04.30	05.00	05.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
l off												
eep												

ID:	Clinic Date:

PATIENT DIARY

Please put an **X** in the correct box for every half-hour period, using the term that best describes your condition during the last few minutes of that half-hour. Only one X should be in each half-hour period. Please fill in every day for three days.

DAY 3

Date completed:

ıe (morning)	6.00	6.30	7.00	7.30	8.00	8.30	9.00	9.30	10.00	10.30	11.00	11.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
ep												

ıe (afternoon)	12.00	12.30	13.00	13.30	14.00	14.30	15.00	15.30	16.00	16.30	17.00	17.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
ep												

ıe (evening)	18.00	18.30	19.00	19.30	20.00	20.30	21.00	21.30	22.00	22.30	23.00	23.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
ep												

ıe (night)	24.00	24.30	01.00	01.30	02.00	02.30	03.00	03.30	04.00	04.30	05.00	05.30
with severe dyskinesia												
with mild dyskinesia												
without dyskinesia												
ial off												
off												
ep												

UNIVERSITY OF CARDIFF

LIFE HISTORY QUESTIONNAIRE

UNIVERSITY OF BRISTOL

General Instructions

Thank you for agreeing to help us in our research. We assume that you have no further questions about the study. If you do, then please contact us (see contact details at the back). Your participation is entirely voluntary and you are free to withdraw at any time without giving any reason. If you complete and return this questionnaire, we assume that you have consented to us using this information for the purpose of research. If you do not wish to take part then please return the unanswered questionnaire.

All the information that you give us will be **COMPLETELY CONFIDENTIAL** and will not be seen by your doctor. Please answer **ALL** the questions to the best of your ability.

For most questions you simply need to tick a box or put a circle around a number.
Here are some questions which have already been filled in as an example:

Some questions will start with a statement and you will be asked to tick the appropriate box

For example, if you would probably visit your general practitioner by car then you would answer the following question like this:

Do you use your car to visit your general practitioner?

Definitely Yes	Probably Yes	Probably No	Definitely No
☐	☑	☐	☐

Some questions will require you to put a circle around the most appropriate number
For example, if you find the appointment system at your general practice works well then you may answer the following question like this:

Do you find it relatively easy to arrange an appointment to see your general practitioner?

Agree strongly 1 (2) 3 4 5 6 7 Disagree strongly

Some questions will require you to write a response on a line

For example, if your age is 73 years then you would complete the following question as follows:
How old are you? ___73___(years)

Section A: Early life

We would like to start by asking you some questions about your early life. If you can't remember the answer then don't worry and simply put a X in the don't know box.

1. When you were a baby

(a) Where were you born? Home ☐ 1 Hospital ☐ 2 Don't know ☐ 3

(b) How much did you weight when you were born? (if you don't know leave this blank) ☐☐ lbs ☐☐ oz

(c) If you cannot recall your weight were you told that you were Below average ☐ 1 Average ☐ 2 Above average ☐ 3

We would like you to think about where you lived for the first 20 years of your life in five year time periods (between birth until 5 years, between 6 to 10 years of age, between 11 to 15 years of age, between 16 to 20 years of age). For each time period, we would like to know some characteristics of your home.

---

2. Was your main home from birth until 5 years

(If you lived in more than one home during this period then answer the question for the home that you stayed in for the **majority** of that time.)

(a) located in a City ☐ 1 Town ☐ 2 Village ☐ 3 rural area ☐ 4

(b) supplied with water from Mains ☐ 1 Public Pump ☐ 2 Well/ own pump ☐ 3 Stream/River ☐ 4

(c) was the toilet indoors ☐ 1 outside ☐ 2

(d) number of bedrooms in house ☐☐

3. Was your main home from 6 until 10 years
(If you lived in more than one home during this period then answer the question for the home that you stayed in for the **majority** of that time.)

(a) located in a — City ☐ 1 — Town ☐ 2 — Village ☐ 3 — rural area ☐ 4

(b) supplied with water from — Mains ☐ 1 — Public Pump ☐ 2 — Well/ own pump ☐ 3 — Stream/River ☐ 4

(c) was the toilet — indoors ☐ 1 — outside ☐ 2

(d) number of bedrooms in house ☐☐

4. Was your main home from 11 until 15 years
(If you lived in more than one home during this period then answer the question for the home that you stayed in for the **majority** of that time.)

(a) located in a — City ☐ 1 — Town ☐ 2 — Village ☐ 3 — rural area ☐ 4

(b) supplied with water from — Mains ☐ 1 — Public Pump ☐ 2 — Well/ own pump ☐ 3 — Stream/River ☐ 4

(c) was the toilet — indoors ☐ 1 — outside ☐ 2

(d) number of bedrooms in house ☐☐

5. Was your main home from 16 until 20 years
(If you lived in more than one home during this period then answer the question for the home that you stayed in for the **majority** of that time.)

(a) located in a — City ☐ 1 — Town ☐ 2 — Village ☐ 3 — rural area ☐ 4

(b) supplied with water from — Mains ☐ 1 — Public Pump ☐ 2 — Well/ own pump ☐ 3 — Stream/River ☐ 4

(c) was the toilet — indoors ☐ 1 — outside ☐ 2

(d) number of bedrooms in house ☐☐

6. As a child (until the age of 15 years) did the home you lived in longest have:

	Yes	No
(a) bathroom?	☐ 1	☐ 2
(b) hot water?	☐ 1	☐ 2
(c) your own bedroom?	☐ 1	☐ 2

7. (a) Did you live on a farm for the first twenty years of your life?

Yes ☐ 1 No ☐ 2

(b) If YES, how many years did you live on the farm ☐☐ years

8. (a) Did your father have a manual or non-manual job when you were a child?

Non-manual ☐ 1 Manual ☐ 2

	Yes	No	Don't Know
(b) Did your household have use of a car when you were a child?	☐ 1	☐ 2	☐ 3

9. As a child did you play or have contact with any of the following animals (please tick one box for each row)

	never or rarely	monthly	weekly	daily
(a) Dog	☐ 1	☐ 2	☐ 3	☐ 4
(b) Cat	☐ 1	☐ 2	☐ 3	☐ 4
(c) Bird (pigeon, budgie etc)	☐ 1	☐ 2	☐ 3	☐ 4
(d) Rabbit/Hamster	☐ 1	☐ 2	☐ 3	☐ 4
(e) Horse	☐ 1	☐ 2	☐ 3	☐ 4
(f) Sheep	☐ 1	☐ 2	☐ 3	☐ 4
(g) Chickens	☐ 1	☐ 2	☐ 3	☐ 4

---

10 (a) **Did you go to a nursery before starting school?**

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

10 (b) **Did you go to day-school or boarding school for your primary school education?**

Day-School ☐ 1 Boarding school ☐ 2

10 (c) **Did you go to day-school or boarding school for your secondary school education?**

Day-School ☐ 1 Boarding school ☐ 2

Section B: Life style habits

12. (a) Have you <u>ever</u> smoked a cigarette, a cigar or a pipe?

Yes ☐ 1 No ☐ 2

IF NO, PLEASE GO TO QUESTION 14 (a) AT THE TOP OF THE NEXT PAGE

(b) Do you smoke cigarettes at all nowadays?
(ONLY ANSWER THIS IF YOU HAVE TICKED THE YES BOX ABOVE)

Yes ☐ 1 No ☐ 2

IF NO, PLEASE GO TO QUESTION 13 (a)

(c) About how many cigarettes a day do you usually smoke?
(ONLY ANSWER THIS IF CURRENT SMOKER)

☐☐ cigarettes

(d) How old where you when you started smoking regularly?

☐☐ years old

PLEASE GO TO QUESTION 14 (a) AT THE TOP OF THE NEXT PAGE

13. (a) How often did you smoke cigarettes in the past?
(ONLY ANSWER THIS IF FORMER SMOKER) *(Please tick **<u>one</u>** box only)*

Regularly, at least once a day	Only occasionally	Never really smoked, just tried them once or twice
☐ 1	☐ 2	☐ 3

IF ONLY OCCASIONALLY OR NEVER REALLY SMOKED SKIP TO QUESTION 14 (a)
(b) About how many cigarettes a day did you regularly smoke?

☐☐ Cigarettes

(c) How old where you when you <u>started</u> smoking regularly?

☐☐ years old

(d) How old where you when you <u>stopped</u> smoking?

☐☐ years old

14. (a) Did your parents smoke when you were a child?

No one smoked	Father	Mother	Both parents smoked
☐ 1	☐ 2	☐ 3	☐ 4

(b) When you were at school did your best friends smoke?

Yes	No
☐ 1	☐ 2

(c) Did your best friends smoke at the time you took up your first job or soon after you left school?

Yes	No
☐ 1	☐ 2

(d) Did your first long term partner or spouse smoke?

Yes	No
☐ 1	☐ 2

We would like to know how much alcohol you used to drink when you were between 20 to 29 years of age. If your drinking habit changed during this ten year period, please answer the questions for the pattern that was the most common over this period.

15. (a) How often would you drink BEER, LAGER, STOUT or CIDER when you were in your twenties? *(Please tick **one** box only)*

Every day	☐ 1	5 or 6 days a week	☐ 2
3 or 4 days a week	☐ 3	Once or twice a week	☐ 4
Once or twice a month	☐ 5	Once every couple of months	☐ 6
Once or twice a year	☐ 7	Not at all	☐ 8

15. (b) When you did have a drink of BEER, LAGER, STOUT, CIDER in your twenties, how many pints would you usually drink at one sitting?
(Please place a number in the box) ☐☐

16. (a) How often would you drink SPIRITS or LIQUERS when you were in your twenties? *(Please tick **one** box only)*

Every day	☐ 1	5 or 6 days a week	☐ 2
3 or 4 days a week	☐ 3	Once or twice a week	☐ 4
Once or twice a month	☐ 5	Once every couple of months	☐ 6
Once or twice a year	☐ 7	Not at all	☐ 8

16. (b) When you did have a drink of SPIRITS or LIQUERS how many pub measures would you usually drink at one sitting?
(Please place a number in the box) ☐☐

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17. (a) How often have you had a drink of SHERRY, MARTINI, PORT, or VERMOUTH when you were in your twenties? *(Please tick **one** box only)*

Every day	☐ 1	5 or 6 days a week	☐ 2
3 or 4 days a week	☐ 3	Once or twice a week	☐ 4
Once or twice a month	☐ 5	Once every couple of months	☐ 6
Once or twice a year	☐ 7	Not at all	☐ 8

17. (b) When you did have a drink of SHERRY, MARTINI, PORT, or VERMOUTH in your twenties, how many small glasses would you usually drink at one sitting?
(Please place a number in the box) ☐☐

18. (a) How often have you had a drink of WINE or CHAMPAGNE when you were in your twenties? *(Please tick **one** box only)*

Every day	☐ 1	5 or 6 days a week	☐ 2
3 or 4 days a week	☐ 3	Once or twice a week	☐ 4
Once or twice a month	☐ 5	Once every couple of months	☐ 6
Once or twice a year	☐ 7	Not at all	☐ 8

18. (b) When you did have a drink of WINE or CHAMPAGNE in your twenties, how many glasses would you usually drink at one sitting:
(Please place a number in the box) ☐☐

PHYSICAL ACTIVITY

19. (a) When you were at school were you in any school sports teams

Yes	No
☐ 1	☐ 2

If YES, which of the following sports did you do?

	Yes	No		Yes	No
(b) Swimming	☐ 1	☐ 2	(c) Football	☐ 1	☐ 2
(d) Rugby	☐ 1	☐ 2	(e) Cricket	☐ 1	☐ 2
(f) Rowing	☐ 1	☐ 2	(g) Boxing	☐ 1	☐ 2
(h) Athletics	☐ 1	☐ 2	(i) Tennis	☐ 1	☐ 2
(j) Other	☐ 1	☐ 2			

(k) IF OTHER, PLEASE SPECIFY SPORT _____

20. (a) After you left school did you participate in any sports club

Yes	No
☐ 1	☐ 2

20. (b) At the age of 20, which of the following best described your level of phsyical activity? Please also consider the amount of physical activity your job involved at that time. *(Please tick **one** box only)*

Very physically active	☐ 1	Fairly physically active	☐ 2
Not very physically active	☐ 3	Not at all physically active	☐ 4

Section C: For women only

21. The following questions are for women only so if you are a man please leave these questions blank and go to *Section D* below

(a) At what age did you start your periods? ☐☐ years

(b) Have your periods stopped? Yes ☐ 1 No ☐ 2

(c) If they have stopped, at what age did they stop (If not stopped then leave blank) ☐☐ years

(d) Did your periods stop naturally or because of an operation? Naturally ☐ 1 Operation ☐ 2

(e) Have you ever taken the oral contraceptive pill? Yes ☐ 1 No ☐ 2

(f) For how long have you taken it (whether you have stopped or are still taking it) ☐☐ years not applicable ☐

(g) Have you ever taken hormone replacement therapy? Yes ☐ 1 No ☐ 2

(h) For how long have you taken it? (whether you have stopped or are still taking it) ☐☐ years not applicable ☐

(i) How many pregnancies, including stillbirths and miscarriages have you had? ☐☐ give number

Section D: Occupational history

The following section covers your employment history

22 (a) Are you currently:

Employed	☐ 1	At home doing housework / caring for family	☐ 2
Retired	☐ 3	Unemployed seeking work	☐ 4
Full-time student	☐ 5	Unemployed through sickness/disability	☐ 6
Doing voluntary work	☐ 7		

---

23. (a) What is/was your main job? If retired or unemployed please describe your main previous employment:

Job title:_____

23. (b) Please describe the main things you do/did in this job:

_____

_____

23. (c) Which one of the following best describes your position in your current or last job (tick ONE box only)

Self employed (25 or more employees)	☐ 1	Manager (less than 25 employees)	☐ 5
Self employed (less than 25 employees)	☐ 2	Supervisor	☐ 6
Self employed (no employees)	☐ 3	Employee	☐ 7
Manager (more than 25 employees)	☐ 4		

23. (d) Would you describe this job as non-manual or manual?

Non-manual ☐ 1 Manual ☐ 2

---

24. Over your career, have you ever worked on a regular basis (once a week or more) with any of the following:

	Yes	No	If YES for how many years?
(a) Lead	☐ 1	☐ 2	☐☐ years
(b) Copper	☐ 1	☐ 2	☐☐ years
(c) Manganese	☐ 1	☐ 2	☐☐ years
(d) Iron	☐ 1	☐ 2	☐☐ years
(e) Wood	☐ 1	☐ 2	☐☐ years
(f) Chemical Solvents	☐ 1	☐ 2	☐☐ years
(g) Paint strippers	☐ 1	☐ 2	☐☐ years
(h) Fertilizers	☐ 1	☐ 2	☐☐ years
(i) Pesticides	☐ 1	☐ 2	☐☐ years

Section E: Past medical history and general well being

25. Have you ever been told by a <u>doctor</u> that you have, or have had, any of the following?

	Yes	No
(a) Angina	☐ 1	☐ 2
(b) Heart Failure *(shortness of breath due to heart problems)*	☐ 1	☐ 2
(c) Stroke / or mini-stroke *(TIA – transient ischaemic attack)*	☐ 1	☐ 2
(d) Heart attack *(coronary thrombosis, myocardial infarction)*	☐ 1	☐ 2
(e) Diabetes	☐ 1	☐ 2
(f) High cholesterol level	☐ 1	☐ 2
(g) High blood pressure	☐ 1	☐ 2
(h) Lung Cancer	☐ 1	☐ 2
(i) Bowel / Colon Cancer	☐ 1	☐ 2
(j) Prostate Cancer	☐ 1	☐ 2
(k) Breast Cancer	☐ 1	☐ 2
(l) Depression	☐ 1	☐ 2
(m) Asthma	☐ 1	☐ 2
(n) Chronic Bronchitis	☐ 1	☐ 2
(o) Emphysema	☐ 1	☐ 2
(p) Other Illness *-please specify:* _____	☐ 1	☐ 2

26. Have you ever had an injury to the head that resulted in any of the following (If more than one episode than enter the age the first time it occurred)

	Yes	No	Age at event
(a) Seizure or fit	☐ 1	☐ 2	(b) ☐☐ years
(c) Dizziness	☐ 1	☐ 2	(d) ☐☐ years
(e) Loss of consciousness	☐ 1	☐ 2	(f) ☐☐ years
(g) Attendance at the Accident and Emergency Dept	☐ 1	☐ 2	(h) ☐☐ years
(i) Admission to hospital	☐ 1	☐ 2	(j) ☐☐ years

The following questions ask for your views about your health and how you feel about life <u>in general</u>. If you are unsure about how to answer any question, try and think about your <u>overall health</u> and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

27. (a) <u>In general</u>, would you say your health is: (Please tick **one** box)

Excellent ☐ 1 Very good ☐ 2

Good ☐ 3 Fair ☐ 4

Poor ☐ 5

(b) <u>Compared to 3 months ago</u>, how would you rate your health in general <u>now</u>?

(Please tick **one** box)

Much better than 3 months ago ☐ 1

Somewhat better than 3 months ago ☐ 2

About the same ☐ 3

Somewhat worse now than 3 months ago ☐ 4

Much worse now than 3 months ago ☐ 5

28. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

(Please tick **one** box on each line)	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b) **Moderate activities,** such as moving a table, pushing a vacuum, bowling or playing golf	☐ 1	☐ 2	☐ 3
c) Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d) Climbing **several** flights of stairs	☐ 1	☐ 2	☐ 3
e) Climbing **one** flight of stairs	☐ 1	☐ 2	☐ 3
f) Bending kneeling or stooping	☐ 1	☐ 2	☐ 3
g) Walking **more than a mile**	☐ 1	☐ 2	☐ 3
h) Walking **half a mile**	☐ 1	☐ 2	☐ 3
i) Walking **100 yards**	☐ 1	☐ 2	☐ 3
j) Bathing and dressing yourself	☐ 1	☐ 2	☐ 3

---

29. (a) During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u>

(Please tick **one** box) on each line	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
a) Cut down on the **amount of time** you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b) **Accomplished less** than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c) Were limited in the **kind** of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d) Had difficulty performing the work or other activities (eg it took more effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

29. **(b) During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

(Please tick **one** box) on each line	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
a) Cut down on the **amount of time** you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b) **Accomplished less** than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c) Didn't do work or other activities as **carefully** as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

---

29 (c) During the <u>past 2 weeks</u>, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbours or groups?

(Please tick **one** box)

- Not at all ☐ 1
- Slightly ☐ 2
- Moderately ☐ 3
- Quite a bit ☐ 4
- Extremely ☐ 5

---

29. (d) How much bodily pain have you had during the <u>past 2 weeks</u> ?

(Please tick **one** box)

- None ☐ 1
- Very mild ☐ 2
- Mild ☐ 3
- Moderate ☐ 4
- Severe ☐ 5
- Very severe ☐ 6

29 (e) During the <u>past 2 weeks</u>, how much did pain interfere with your normal work (including both outside the home and housework)?

(Please tick **one** box)

- Not at all ☐ 1
- Slightly ☐ 2
- Moderately ☐ 3
- Quite a bit ☐ 4
- Extremely ☐ 5

---

30. These questions are about how you feel and how things have been with you during the <u>past 2 weeks</u>. For each question please give one answer that comes closest to the way you have been feeling.
(Please tick **one** box) on each line

	How much time during <u>the last 2 weeks:</u>	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a)	Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b)	Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c)	Have you felt so down in the dumps that nothing would cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d)	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e)	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f)	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g)	Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h)	Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
i)	Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

31. During the <u>past 2 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives etc.).

(Please tick **one** box)

- All of the time ☐ 1
- Most of the time ☐ 2
- Some of the time ☐ 3
- A little of the time ☐ 4
- None of the time ☐ 5

---

32. How TRUE or FALSE is <u>each</u> of the following statements for you?

(Please tick **one** box on each line)

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a)	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b)	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c)	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d)	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

33. Please use the scoring system below to rate how likely you are in each of the following situations to fall off to sleep. This should refer to how you have usually felt recently.

SITUATION	CHANCE OF DOZING OFF			
	NO chance	SLIGHT chance	MODERATE chance	HIGH chance
(a) Sitting and reading	☐ 1	☐ 2	☐ 3	☐ 4
(b) Watching TV	☐ 1	☐ 2	☐ 3	☐ 4
(c) Sitting inactive in a public place e.g. theatre, meeting	☐ 1	☐ 2	☐ 3	☐ 4
(d) As a passenger in a car for an hour without a break	☐ 1	☐ 2	☐ 3	☐ 4
(e) Lying down to rest in the afternoon	☐ 1	☐ 2	☐ 3	☐ 4
(f) Sitting and talking to someone	☐ 1	☐ 2	☐ 3	☐ 4
(g) Sitting quietly after lunch (when you've had **no** alcohol)	☐ 1	☐ 2	☐ 3	☐ 4
(h) In a car, whilst stopped for a few minutes in traffic	☐ 1	☐ 2	☐ 3	☐ 4

Section F: Family History

34. (a) **Are your parents related in anyway?**

Yes ☐ 1 No ☐ 2

34 (b) **If YES in what way e.g. first cousin**

_____

35 **Where was your father born?**

(a) Town:_____ (b) County:_____

36 **Where was your mother born?**

(a) Town:_____ (b) County:_____

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37. **The following questions help us to determine your family size**

(a) How many brothers were there in your family (include half-brothers if appropriate) ☐☐ no. of brothers

(b) How many sisters were there in your family (include half-sisters if appropriate) ☐☐ no. of sisters

(c) How many of your brothers and sisters were older than you? (If you are the first born then please enter the number 0) ☐☐ no. of older siblings

(d) How many brothers did your **mother** have in her family (include half-brothers if appropriate) ☐☐ no. of maternal brothers

(e) How many sisters did your **mother** have in her family (include half-sisters if appropriate) ☐☐ no. of maternal sisters

(f) How many brothers did your **father** have in his family (include half-brothers if appropriate) ☐☐ no. of paternal brothers

(g) How many sisters did your **father** have in his family (include half-sisters if appropriate) ☐☐ no. of paternal sisters

38. **Did any member of your family (parents, brothers, sisters, uncles or aunts) ever have a tremor of their hands which was present when their hands were resting? (Record the number of any such relative(s) in the relevant box below, for example if 1 maternal uncle had a tremor you should enter the number 1 in that box; if none of your maternal uncles had a tremor, please enter 0.)**

(a) Father	☐	(b) Mother	☐
(c) Brothers	☐	(d) Sisters	☐
(e) Maternal Uncles	☐	(f) Maternal Aunts	☐
(g) Paternal Uncles	☐	(h) Paternal Aunts	☐

39. **Did any member of your family (parents, brothers, sisters, uncles or aunts) have a diagnosis of Parkinson's disease? (Record the number of any such relative(s) in the relevant box below, for example if 1 maternal uncle had Parkinson's disease you should enter the number 1 in that box; if none of your maternal uncles had Parkinson's disease, please enter 0.)**

(a) Father	☐	(b) Mother	☐
(c) Brothers	☐	(d) Sisters	☐
(e) Maternal Uncles	☐	(f) Maternal Aunts	☐
(g) Paternal Uncles	☐	(h) Paternal Aunts	☐

Section G: Further background information

40. Are you? Male ☐ 1 Female ☐ 2

41. Date of birth: _____ (day) /_____ (month) / _____ (year)

42. Where were you born?

Wales	☐ 1	South Africa	☐ 9
England	☐ 2	Middle East	☐ 10
Scotland	☐ 3	India	☐ 11
N. Ireland	☐ 4	Pakistan	☐ 12
Republic of Ireland	☐ 5	Bangladesh	☐ 13
Caribbean	☐ 6	Far East	☐ 14
East Africa	☐ 7	Other	☐ 15
West Africa	☐ 8		

43. (b) If other please specify: _____

44. (a) What is your religion, if any? (please tick the most appropriate answer)

Christian (Church of England, Catholic, Protestant, and other denominations)	☐ 1	Sikh	☐ 5
Buddhist	☐ 2	Jewish	☐ 6
Hindu	☐ 3	None (atheist/agnostic)	☐ 7
Muslim	☐ 4	Other	☐ 8

44. (b) If other please specify: _____

45. Please tick the box that most accurately describes your ethnic origin

(A) White

British ☐ 1

Welsh ☐ 17

Irish ☐ 2

Any other White background ☐ 3

please state_____

(B) Black or Black British

Caribbean ☐ 4

African ☐ 5

Any other Black background ☐ 6

please state_____

(C) Mixed

White and Black Caribbean ☐ 7

White and Asian ☐ 8

White and Black African ☐ 9

Other mixed background ☐ 10

please state_____

(D) Asian or Asian British

Indian ☐ 11

Bangladeshi ☐ 12

Pakistani ☐ 13

Other Asian background ☐ 14

please state_____

(E) Chinese or other ethnic group

Chinese ☐ 15

Other ☐ 16

Please state_____

46. (a) How old were you when you left school? _____ years

46. (b) Have you had any full or part time further or higher education since you left school?

YES ☐ 1 NO ☐ 2

If there are any other comments you would like to make please write them here:

Name of the participant _____

Address _____

_____

Postcode _____

Thank you for filling in this questionnaire

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REVIEW ARTICLE

The effect of onset age on the clinical features of Parkinson's disease

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Many clinicians view age at onset as an important determinant of clinical phenotype in Parkinson's disease (PD) and this has been reinforced by the identification of Mendelian genes that account for some cases of younger onset PD. A systematic review of OVID Medline for articles relevant to the relationship between clinical features and age at onset in PD published in English between 1950–2007 was performed. There are very few prospective community based studies which focus on the relationship between age at onset and the features of PD and a variety of case definitions are used in the literature. Most studies of young onset PD are based on specialist clinic referral series. The available evidence suggests that PD patients with a younger age at onset have: (i) a slower disease progression, (ii) an increased rate of dystonia at onset and during treatment, (iii) a lower rate of dementia and (iv) an increased rate of dyskinesias in response to L-DOPA treatment. The majority of the available studies do not report patient genotype data, but it is probably that the clinical heterogeneity of PD will be further refined with detailed clinico-genetic studies.

Introduction

Historically, Parkinson's disease (PD) has been defined by the clinical features of pathologically diagnosed Lewy body disease with loss of nigro-striatal neurones and the presence of alpha-synuclein containing Lewy bodies [1]. The risk of developing PD is age dependant, and affects 1–2% of the population over 65 years [2,3]. The relationship between PD and age suggests that cumulative exposure to an environmental factor, and/or an age dependant biological factor, determines its development. The Kaiser Permanente study identified an incidence of 1.5/100 000 person years in the under-50s, compared with 13.4 per 100 000 overall, and in a prevalent PD population 0.9% of patients developed PD before the age of 40, and 5.4% before the age of 50 [2,4,5]. The identification of Mendelian genes which can cause typical parkinsonism with young onset and reports of pathological heterogeneity raise the possibility that young onset PD (YOPD) may be different to late onset PD (LOPD) [6–8]. If this is the case then the advice and treatment given to patients, in particular future disease modifying therapies may need to be tailored according to the age of onset and related parkinsonism/PD sub-type. The disease entity of PD has been defined by the presence of Lewy bodies, but only a minority of patients go on to have post-mortem analysis. Lewy body pathology is rare in patients with parkin mutations having been reported in 2/6 cases [9–14]. A brain bank series of 12 YOPD patients (onset before 40 years) and 24 LOPD patients (onset after 70 years) showed no difference in the occurrence of Lewy body pathology [15], and it is not known whether YOPD patients as a whole frequently have non-Lewy body pathology.

Here, we review the evidence for the separation of PD and parkinsonism based on age at onset specifically looking at the following clinical questions: (i) do YOPD patients have slower or faster disease progression than LOPD patients, (ii) do YOPD patients have a different rate of tremor at presentation or during the disease course, (iii) do YOPD patients have an increase in dystonia, (iv) do YOPD patients have an increase in susceptibility to dyskinesias and (v) do YOPD patients have a lower or higher rate of dementia. We review the evidence relating to these issues and identify some of the problems in interpreting the available data.

Methods

Search strategy

This review is based on a literature search of the English language Ovid Medline databases spanning 1950–2007 using: PD, parkinsonian syndrome, parkinsonism, paralysis agitans, and akinetic-rigid syndrome, combined with young onset, early onset, age at onset and juvenile onset. We have also used the authors' personal databases and hand searching of references. We used the search terms 'Parkinson's disease', 'parkinsonian syndrome', 'parkinsonism', 'paralysis agitans', and

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'akinetic-rigid syndrome', limited articles to the English language and combined with the search terms 'young onset', 'early onset', 'age at onset' and 'juvenile onset'. This yielded 1526 articles. The abstracts of these were reviewed for relevance to the questions set in this review. Including both review articles and original data papers led to 376 articles, potentially relevant to this review. Papers including data relevant to the selected research questions were analysed including analysis of confidence intervals and significance of reported differences between groups.

Case definition

The initial difficulty in reviewing YOPD is case definition. The terms juvenile, young and early onset have all been used to describe YOPD with inconsistent definitions. [16–21]. In 1987, Quinn and colleagues suggested that 'juvenile onset parkinsonism' should be reserved for cases with onset before the age of 21, and 'young onset' for patients with onset between 21 and 40 years [22,23]. More recent papers, including those reviewing genetic factors, have used the term early onset to describe PD occurring before the age of 45. Other have used cut-offs of up to 70 years to define clinical differences. Since many different ages of onset have been used to define YOPD, in this review we use YOPD to indicate the younger onset comparative group and define the age at onset where possible.

Results

Disease progression and quality of life

Variations in measures of disease progression make direct comparison between studies difficult (Tables S1 and S2). The majority of studies are retrospective [24,25]. Two methods have been used – comparing progression in two groups defined by age at onset [24,26,27], or comparing mean age at onset in groups defined by rate of progression [24,26,28–30]. The Sydney Multi-Centre Study group concluded that age at onset was the best predictor of deterioration in PD over 5 years (younger onset, slower progression) [24,25]. In the DATATOP study, a retrospective estimate of progression showed more rapid progression in LOPD (onset at or above age 70) than YOPD (onset at or before age 40) [26]. Three further studies have confirmed that YOPD has a slower disease progression (Tables S1 and S2) [27–29]. Conflicting views have been reported, using different methods. In a study of 60 YOPD (onset <40 years) and 60 LOPD (onset 42–68 years) patients estimating disease progression as the interval from first symptom onset to the development of a bilateral clinical picture, 60% of the YOPD group developed bilateral involvement within 12 months of onset compared with 5% of the LOPD group [16]. This may reflect earlier bilateral involvement in YOPD but the relatively short follow-up period in this study means that it is difficult to generalize this finding. The majority of studies of YOPD are based on specialist clinic case ascertainment; therefore a further possible confounding factor is case referral bias. Elderly patients with indolent disease may be treated by their non-specialist family practitioners, rather than being referred to specialist clinics, although this will vary in different health care systems. On balance, the majority of the evidence from retrospective clinic based series supports a slower disease progression in YOPD as compared with LOPD.

Whilst slower disease progression may be a source of some reassurance for younger onset patients, the relative effect of PD on mortality and absolute effect on life expectancy is more marked in YOPD. A previous population-based cohort study of patients with parkinsonism noted that the standardized mortality ratio for cases aged 40–50 years at onset was 3.9 (almost four times that of the general population) compared with 2.0 for cases aged between 75 and 84 years [31]. The interpretation of this figure requires caution however, as it may include patients with multiple system atrophy and progressive supranuclear palsy [32]. A recent literature review [33] estimated that the life expectancy of patients with onset between 25 and 39 years was 38 years compared with 49 years in the general population resulting in a relative loss of 22% but in absolute terms 11 years of life. The equivalent figures for cases with onset older than 64 years was 5 compared with 9 years in the general population, which is 44% in relative terms but a 4-year loss of survival in absolute terms. There may also be a differential impact on quality of life in YOPD. A survey of YOPD and LOPD patients indicates that despite similar disease severity, YOPD patients have poorer quality of life and are much more probably to retire early [34]. Thus, young onset disease is associated with more years of worsened quality of life and late onset disease, in contrast, shows a relative 'compression of morbidity'. Evidence from preference studies suggest that the general public rate past years of ill-health and young age at onset as more important in terms of allocating treatments [35].

Parkinsonian symptoms at presentation and dominant motor phenotype

Parkinson's disease can be tremor-dominant or postural instability with gait disorder dominant [26].

Several studies have associated motor phenotype with rate of progression. Tremor dominance both at presentation and after 2–7 years from onset are associated with slower progression [26,36–41]. It has been suggested that 'benign tremulous parkinsonism' is a separate clinical entity with prominent tremor not responding well to L-dopa, and minimal progression of other aspects of parkinsonism [42]. There is no consensus on tremor frequency in YOPD having been reported less, more and equally as frequently as LOPD (Table 1) [15,16,24,37,43–46]. YOPD patients are less probably to have gait disturbance as an early symptom (Table S3) [15,44,46]. This may reflect the confounding effects of age and co-morbidity. Observations may also be biased due to referral and diagnosis – the presence of tremor is probably to have a significant effect on management by non-specialists. A community based study in the UK showed that 16% of patients who developed tremor after the age of 55, diagnosed in the community with non-parkinsonian tremor, met the criteria for probable PD [47]. Younger onset patients are more probably to be referred to specialists, so tremulous PD may be underrepresented in the later onset group because of misdiagnosis in primary care, although this will depend on local health care systems. The available data suggest that patients with YOPD have less gait difficulty early in the disease course than LOPD patients but there is no clear conclusion regarding the frequency of tremor dominant disease.

Table 1 Disease features at onset

Study	*n* (YOPD/LOPD)	AAO YOPD (years)	Source of patients	Clinical feature	YOPD versus LOPD	Difference (%), (95% CI) *P*-value	Conclusions
Gibb [15]	46/52	< 45	Clinic	Tremor	41% vs. 63%	−22, (−41, −3) $P = 0.03$	Tremor at onset commoner in LOPD
Hely [24]	90/33	< 70	Sydney RCT	Tremor	42% vs. 64%	−22, (−41, −3) $P = 0.03$	Tremor at onset commoner in LOPD
Freidman [43]	44/46	< 47	Clinic	Tremor	34% vs. 59%	−25 (−45, −5) $P = 0.02$	Tremor at onset commoner in LOPD
Kostic [44]	25/25	< 40	Clinic	Tremor	32% vs. 36%	−4, (−30, 22) $P = 0.76$	Marginal difference
Quinn [23]	56/–	< 40	Clinic	Tremor	52%		52% of YOPD had tremor at onset
Gomez [46]	34/34	< 40	Clinic	Tremor	44% vs. 46.4%	−2 (−26, 21) $P = 0.84$	Marginal difference
Giovannini [16]	60/60	< 40	Clinic	Tremor	35% vs. 21.7%	13 (−3, 29) $P = 0.11$	Tremor at onset commoner in YOPD but could be chance
Pantelatos [45]	221/1511	< 40	Hospital	Tremor	No difference (no figures given)		No difference
Gibb [15]	46/52	< 45	Clinic	Gait	4% vs. 63%	− 59 (−73, −45) $P < 0.0001$	Gait difficulty at onset less common in YOPD
Gomez [46]	34/34	< 40	Clinic	Gait	2.7% vs. 38.8%	−36 (−53, −19) $P = 0.0002$	Gait difficulty at onset less common in YOPD
Kostic [44]	25/25	< 40	Clinic	Gait	4% vs. 16%	−12 (−28, 4) $P = 0.16$	Gait difficulty at onset less common in YOPD

AAO, Age at onset; YOPD, young onset Parkinson's disease; LOPD, late onset Parkinson's disease; RCT, randomized control trial.

Dystonia

Dystonia can occur either pre-treatment, or on treatment as peak-dose or off-period motor features [48]. Limb dystonia related to exercise can be a striking feature of YOPD and has been reported to be frequent in Japanese and other patients with autosomal recessive juvenile parkinsonism subsequently found to have *parkin* mutations [49–52]. Dystonia at onset is presumably an alternative manifestation of dopamine deficiency in YOPD and occurs with a frequency of between 14% and 57% (Table 2). Painful off period dystonia, particularly affecting the feet and ankles is also more common in patients with YOPD occurring at a rate of 30–59% during treatment [15,23].

Dementia and neuropsychiatric features

Cognitive impairment and neuro-psychiatric side effects to medication are less frequent in YOPD. A large body of evidence suggests LOPD patients are at a higher risk of dementia [26,37,39,53–56], and that the incidence of dementia in YOPD aged under 65 years is negligible

Table 2 Dystonia

Study	*n* (YOPD/ LOPD)	YOPD age (years)	Source	Dystonia at onset YOPD versus LOPD (95% CI for difference)	Treatment dystonia YOPD versus LOPD	Conclusions
Gomez [46]	34/34	< 40	Clinic	30.5% vs. 0% (95% CI 15, 46) $P = 0.0005$		Dystonia at onset commoner in YOPD
Tanner [75]	21/21	< 55	Clinic	57% vs. 10% (95% CI 22, 72) $P = 0.001$		Dystonia at onset commoner in YOPD
Gibb [15]	46/52	< 45	Clinic	4.3% vs. 0% (95% CI −2, 10) $P = 0.13$	33% vs. 0% (95% CI 19, 47) $P < 0.0001$	
Quinn[23]	56/–	< 40	Clinic	14%	59%	Treatment related dystonia in nearly 2/3 of YOPD
Gershanik [18]	18/–	< 40	Clinic	53%		Dystonia at onset in over half of YOPD
Gershanik [17]	30/–		Clinic		50%	Treatment related dystonia in over half of YOPD
Kidron [48]	207		Clinic	Early morning dystonia AAO = 53.4 years. Off period dystonia AAO = 50 years. No dystonia AAO = 60.9 years.		

YOPD, young onset Parkinson's disease; LOPD, later onset Parkinson's disease; AAO, age at onset; CI, confidence interval.

[23,24,26,55,57–63]. However, there may be evidence of subtle cognitive involvement in YOPD [55,57]. In the CAMPAIGN study of patients defined by the UK Brain Bank criteria, older age at onset is a risk factor for developing cognitive impairment, although in this study only one patient had disease onset before 40 years [64]. Studies comparing the rates of dementia in PD patients with age matched non-PD controls suggest that patients with PD have significantly higher risk of developing dementia, and age at onset of PD was reported as a determinant of developing dementia in these patients [65–68]. In a population based study of PD the percentage of patients with dementia increased with age but the prevalent PD cases with and without dementia did not differ in disease duration suggesting that age rather than disease duration influences the prevalence of dementia [60].

Treatment response and related complications

It has been widely reported that YOPD patients have an excellent response to L-DOPA treatment, marred by the early development of treatment related dyskinesias and motor complications (Table 3) [15,16,18,23,24,44,53,54,69]. Studies comparing differences in treatment response are confounded by delay in L-DOPA treatment in YOPD patients, differences in total L-DOPA dosage and the use of concurrent dopamine agonists. In an attempt to overcome this Kostic and colleagues carried out a carefully designed study of YOPD (onset between 21 and 40 years) and LOPD (onset >40 years); matched for gender, duration of disease, mode of onset, Hoehn and Yahr stage, duration of treatment and dose of L-DOPA [44]. Twenty-five patients were identified in each group. This small study showed a significantly higher frequency of both dyskinesias and response fluctuations in the YOPD group. A further population based study showed a higher 5-year dyskinesia incidence with younger age at onset (50% in those with onset <60 years, and 16% in those with onset >70 years) but did not include any patients with onset before age 40 years [70]. Clinical series data suggest that patients with YOPD develop dyskinesias earlier than LOPD patients but the impact on quality of life, and age thresholds are not clearly defined.

Discussion

Most PD studies report current age rather than age at onset, involve small numbers of patients, include highly selected specialty clinic based populations and are subject to variation in methodology which causes difficulty in comparison across studies and introduces

Table 3 Dyskinesia and motor fluctuations

Study	*n* (YOPD/ LOPD)	YOPD age (years)	Source of patients	Dyskinesia YOPD	Dyskinesia LOPD	Fluctuations YOPD	Fluctuations LOPD
Yokoshi [20]	32/–	< 40		32%			
Quinn [23]	56/–	< 40	Clinic	55% at 1 year 100% at 6 years			
Perderzoli [54]				Increased			
Tanner [75]				91%			
Gibb [15]	46/52	< 45	Clinic	91%			
Gershanik [18]				75%			
Kostic [44]	25/25			72% at 3 years*	28% at 3 years	64% at 3 years**	28% at 3 years
Hely [24]	90/33	< 70	Sydney Multicentre trial (referral)	No differences			
Barbeau [76]	32	< 40		42% at 2 years		35% at 2 years	
Kumar [70]	5/–	< 50	Population	40% at 5 years	28% at 5 years		

YOPD, young onset Parkinson's disease; LOPD, later onset Parkinson's disease.
*P-value for difference = 0.002.
**P-value for difference = 0.01.

potential biases. Variation in methodology include inclusion/diagnostic criteria, age definitions and disability measures. The available evidence suggests that patients with YOPD have (i) a slower disease progression, (ii) more frequent dystonia at onset, (iii) more frequent early dyskinesias in response to L-DOPA treatment, (iv) less frequent gait disturbance and (v) less frequent dementia. Amongst these differences the dystonia at onset is often seen in YOPD (4–57% of cases) and is uncommon in LOPD. Dyskinesias as an early complication of L-DOPA therapy are appreciably more common in YOPD with an approximate doubling of the risk of dyskinesias at between 3 and 5 years. YOPD is probably to comprise a heterogeneous patient group, related to genetic aetiology. Approximately 9–20% of early onset PD patients have mutations in the parkin gene with a further 1% of cases related to mutations in the PINK1 and DJ-1 genes. Mutation frequencies vary with population ascertainment and age at onset [8,50,71–74] . Some YOPD patients may have a different disease based on genetic aetiology and specific pathology but this has not been established in a community based, pathologically confirmed sample. There is currently little direct evidence to support patho-physiological difference between 'non-genetic' YOPD and LOPD. It is probably that the definition of further genetic risk factors and biomarkers will lead to a fuller definition of the heterogeneity of PD. Ultimately this should lead to a more directly patient-centred approach to PD management, with specific advice on familial risk, prognosis, likelihood of disease related complications and appropriate disease modifying therapies based on genetic background and age at onset.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Disease Progression YOPD versus LOPD.
Table S2. Disease progression – Other analysis methods.

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References

1. Litvan I, Bhatia KP, Burn DJ, *et al.* Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Movement Disorders* 2003; **18:** 467–486.
2. Van Den Eeden SK, Tanner CM, Bernstein AL, *et al.* Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American Journal of Epidemiology* 2003; **157:** 1015–1022.
3. de Rijk MC, Tzourio C, Breteler MM, *et al.* Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. *Journal of Neurology, Neurosurgery and Psychiatry* 1997; **62:** 10–15.
4. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. *Lancet Neurology* 2006; **5:** 355–363.
5. Wickremaratchi M, Perera D, O'Loghlen C, *et al.* Prevalence and age at onset of Parkinson's disease in Cardiff – a community based cross-sectional study and meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry* (in press).
6. Morris HR. Genetics of Parkinson's disease. *Annals of Medicine* 2005; **37:** 86–96.

7. Hardy J, Cai H, Cookson MR, Gwinn-Hardy K, Singleton A. Genetics of Parkinson's disease and parkinsonism. *Annals of Neurology* 2006; **60:** 389–398.
8. Klein C, Lohmann-Hedrich K, Rogaeva E, Schlossmacher MG, Lang AE. Deciphering the role of heterozygous mutations in genes associated with parkinsonism. *Lancet Neurology* 2007; **6:** 652–662.
9. Hayashi S, Wakabayashi K, Ishikawa A, *et al.* An autopsy case of autosomal-recessive juvenile parkinsonism with a homozygous exon 4 deletion in the parkin gene. *Movement Disorders* 2000; **15:** 884–888.
10. Farrer M, Chan P, Chen R, *et al.* Lewy bodies and parkinsonism in families with parkin mutations. *Annals of Neurology* 2001; **50:** 293–300.
11. Sasaki S, Shirata A, Yamane K, Iwata M. Parkin-positive autosomal recessive juvenile Parkinsonism with alpha-synuclein-positive inclusions. *Neurology* 2004; **63:** 678–682.
12. Pramstaller PP, Schlossmacher MG, Jacques TS, *et al.* Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. *Annals of Neurology* 2005; **58:** 411–422.
13. van de Warrenburg BP, Lammens M, Lucking CB, *et al.* Clinical and pathologic abnormalities in a family with parkinsonism and parkin gene mutations. *Neurology* 2001; **56:** 555–557.
14. Mori H, Kondo T, Yokochi M, *et al.* Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q. *Neurology* 1998; **51:** 890–892.
15. Gibb WR, Lees AJ. A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. *Neurology* 1988; **38:** 1402–1406.
16. Giovannini P, Piccolo I, Genitrini S, *et al.* Early-onset Parkinson's disease. *Movement Disorders* 1991; **6:** 36–42.
17. Gershanik OS, Nygaard TG. Parkinson's disease beginning before age 40. *Advances in Neurology* 1990; **53:** 251–258.
18. Gershanik OS, Leist A. Juvenile onset Parkinson's disease. *Advances in Neurology* 1987; **45:** 213–216.
19. Yokochi M, Narabayashi H, Iizuka R, Nagatsu T. Juvenile parkinsonism – some clinical, pharmacological, and neuropathological aspects. *Advances in Neurology* 1984; **40:** 407–413.
20. Yokochi M, Narabayashi H. *Clinical Characteristics of Juvenille Parkinsonism.* Tumbridge Wells: Pitman medical, 1981.
21. Yokochi M. Familial juvenile parkinsonism. *European Neurology* 1997; **38**(Suppl. 1)**:** 29–33.
22. Jankovic J, Tolosa E. *Parkinson*'s Disease and Related Disorders, 2nd edn. Baltimore: Williams & Wilkins, 1993.
23. Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. *Movement Disorders* 1987; **2:** 73–91.
24. Hely MA, Morris JG, Reid WG, *et al.* Age at onset: the major determinant of outcome in Parkinson's disease. *Acta Neurologica Scandinavica* 1995; **92:** 455–463.
25. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muenter MD. Effect of age at onset on progression and mortality in Parkinson's disease. *Neurology* 1989; **39:** 1187–1190.
26. Jankovic J, McDermott M, Carter J, *et al.* Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology* 1990; **40:** 1529–1534.
27. Lee CS, Schulzer M, Mak EK, *et al.* Clinical observations on the rate of progression of idiopathic parkinsonism. *Brain* 1994; **117:** 501–507.
28. Birkmayer W, Riederer P, Youdin MBH. Distinction between benign and malignant type of Parkinson's disease. *Clinical Neurology and Neurosurgery* 1979; **81:** 158–164.
29. Goetz CG, Tanner CM, Stebbins GT, Buchman AS. Risk factors for progression in Parkinson's disease. *Neurology* 1988; **38:** 1841–1844.
30. Marttila RJ, Rinne UK. Disability and progression in Parkinson's disease. *Acta Neurologica Scandinavica* 1977; **56:** 159–169.
31. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58:** 293–299.
32. Nath U, Thomson R, Wood R, *et al.* Population based mortality and quality of death certification in progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76:** 498–502.
33. Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. *Journal of Neurology, Neurosurgery and Psychiatry* 2007; **78:** 1304–1309.
34. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Young- versus older-onset Parkinson's disease: impact of disease and psychosocial consequences. *Movement Disorders* 2003; **18:** 1250–1256.
35. Dolan P, Tsuchiya A. Health priorities and public preferences: the relative importance of past health experience and future health prospects. *Journal of Health Economics* 2005; **24:** 703–714.
36. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; **17:** 427–442.
37. Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. *Neurology* 1985; **35:** 522–526.
38. Huber SJ, Paulson GW, Shuttleworth EC. Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1988; **51:** 855–858.
39. Biggins CA, Boyd JL, Harrop FM, *et al.* A controlled, longitudinal study of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1992; **55:** 566–571.
40. Schwab RS, England AC, Peterson E. Akinesia in Parkinson's disease. *Neurology* 1959; **9:** 65–72.
41. Hershey LA, Feldman BJ, Kim KY, Commichau C, Lichter DG. Tremor at onset. Predictor of cognitive and motor outcome in Parkinson's disease? *Archives of Neurology* 1991; **48:** 1049–1051.
42. Josephs KA, Matsumoto JY, Ahlskog JE. Benign tremulous parkinsonism. *Archives of Neurology* 2006; **63:** 354–357.
43. Friedman A. Old-onset Parkinson's disease compared with young-onset disease: clinical differences and similarities. *Acta Neurologica Scandinavica* 1994; **89:** 258–261.
44. Kostic V, Przedborski S, Flaster E, Sternic N. Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. *Neurology* 1991; **41:** 202–205.

45. Pantelatos A, Fornadi F. Clinical features and medical treatment of Parkinson's disease in patient groups selected in accordance with age at onset. *Advances in Neurology* 1993; **60:** 690–697.
46. Gomez Arevalo G, Jorge R, Garcia S, Scipioni O, Gershanik O. Clinical and pharmacological differences in early- versus late-onset Parkinson's disease. *Movement Disorders* 1997; **12:** 277–284.
47. Schrag A, Ben-Shlomo Y, Quinn N. How valid is the clinical diagnosis of Parkinson's disease in the community? *Journal of Neurology, Neurosurgery and Psychiatry* 2002; **73:** 529–534.
48. Kidron D, Melamed E. Forms of dystonia in patients with Parkinson's disease. *Neurology* 1987; **37:** 1009–1011.
49. Bozi M, Bhatia KP. Paroxysmal exercise-induced dystonia as a presenting feature of young-onset Parkinson's disease. *Movement Disorders* 2003; **18:** 1545–1547.
50. Khan NL, Graham E, Critchley P, *et al.* Parkin disease: a phenotypic study of a large case series. *Brain* 2003; **126:** 1279–1292.
51. Yamamura Y. Clinical, pathologic and genetic studies on autosomal recessive early-onset parkinsonism with diurnal fluctuation. *Parkinsonism & Related Disorders* 1998; **4:** 65–72.
52. Yamamura Y, Sobue I, Ando K, Iida M, Yanagi T. Paralysis agitans of early onset with marked diurnal fluctuation of symptoms. *Neurology* 1973; **23:** 239–244.
53. Granerus AK, Carlsson A, Svanborg A. The ageing neurone – influence on symptomatology and therapeutic response in Parkinson's syndrome. *Advances in Neurology* 1979; **24:** 327–334.
54. Pederzoli M, Girotti F, Scigliano G, Aiello G, Carella F, Caraceni T. L-dopa long-term treatment in Parkinson's disease: age-related side effects. *Neurology* 1983; **33:** 1518–1522.
55. Hietanen M, Teravainen H. The effect of age of disease onset on neuropsychological performance in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1988; **51:** 244–249.
56. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JA, Mutch WJ. Clinical features predicting dementia in idiopathic Parkinson's disease: a follow-up study. *Neurology* 1990; **40:** 1222–1224.
57. Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y. Age-induced cognitive disturbances in Parkinson's disease. *Neurology* 1990; **40:** 38–41.
58. Elizan TS, Sroka H, Maker H, Smith H, Yahr MD. Dementia in idiopathic Parkinson's disease. Variables associated with its occurrence in 203 patients. *Journal of Neural Transmission* 1986; **65:** 285–302.
59. Lieberman A, Dziatolowski M, Kupersmith M, *et al.* Dementia in Parkinson disease. *Annals of Neurology* 1979; **6:** 355–359.
60. Mayeux R, Denaro J, Hemenegildo N, *et al.* A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. *Archives of Neurology* 1992; **49:** 492–497.
61. Portin R, Rinne UK. Predictive factors for cognitive deterioration and dementia in Parkinson's disease. *Advances in Neurology* 1987; **45:** 413–416.
62. Reid WG, Broe GA, Hely MA, *et al.* The neuropsychology of de novo patients with idiopathic Parkinson's disease: the effects of age of onset. *International Journal of Neuroscience* 1989; **48:** 205–217.
63. Stern Y, Marder K, Tang MX, Mayeux R. Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology* 1993; **43:** 1690–1692.
64. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004; **127:** 550–560.
65. Akinyemi RO, Okubadejo NN, Akinyemi JO, Owolabi MO, Owolabi LF, Ogunniyi A. Cognitive dysfunction in Nigerians with Parkinson's disease. *Movement Disorders* 2008; **23:** 1378–1383.
66. Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Movement Disorders* 2004; **19:** 1043–1049.
67. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology* 2001; **56:** 730–736.
68. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Archives of Neurology* 2003; **60:** 387–392.
69. de Jong GJ, Meerwaldt JD, Schmitz PI. Factors that influence the occurrence of response variations in Parkinson's disease. *Annals of Neurology* 1987; **22:** 4–7.
70. Kumar N, Van Gerpen JA, Bower JH, Ahlskog JE. Levodopa-dyskinesia incidence by age of Parkinson's disease onset. *Movement Disorders* 2005; **20:** 342–344.
71. Lucking CB, Durr A, Bonifati V, *et al.* Association between early-onset Parkinson's disease and mutations in the parkin gene. *New England Journal of Medicine* 2000; **342:** 1560–1567.
72. Hedrich K, Eskelson C, Wilmot B, *et al.* Distribution, type, and origin of Parkin mutations: review and case studies. *Movement Disorders* 2004; **19:** 1146–1157.
73. Klein C, Djarmati A, Hedrich K, *et al.* PINK1, Parkin, and DJ-1 mutations in Italian patients with early-onset parkinsonism. *European Journal of Human Genetics* 2005; **13:** 1086–1093.
74. Kann M, Jacobs H, Mohrmann K, *et al.* Role of parkin mutations in 111 community-based patients with early-onset parkinsonism. *Annals of Neurology* 2002; **51:** 621–625.
75. Tanner CM, Kinouri I, Goertz CG, *et al.* Clinical course in Parkinson's disease: relationship to age at onset. *Journal of Neurology* 1985; **232**(Suppl.)**:** 25.
76. Barbeau A, Pourcher E. New data on the genetics of Parkinson's disease. *Canadian Journal of Neurological Sciences* 1982; **9:** 53–60.

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Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis

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Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis

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► Appendices 1 and 2 and an additional figure and table are published online only at http://jnnp.bmj.com/content/vol80/issue7

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ABSTRACT

Background: Previous prevalence studies of Parkinson's disease (PD) in the UK have spanned a 40 year period and have predominantly been in the North of the country. These have presented rates by current age but have not examined this by age at disease onset.

Methods: A community based prevalence study was undertaken which attempted to identify all clinically diagnosed cases of PD from primary and secondary care for the city of Cardiff, Wales, UK. A meta-analysis of all past studies in the UK, including our own, was also undertaken.

Results: Overall, 380 cases of PD were identified from a population of 292 637 residents, giving a crude prevalence rate of 130 per 100 000 (95% CI 117 to 144) and an age standardised rate of 142 per 100 000 (95% CI 128 156), standardised to the 1997 England and Wales population. Our prevalence rates were very similar to the weighted average of previous UK studies although there was evidence of between study heterogeneity ($p = 0.0006$). 5.4% and 31.2% of prevalent PD patients had their disease onset below the age of 50 or 65 years, respectively.

Conclusions: The data suggest that there are no major geographical variations in the prevalence of PD in the UK and that the age adjusted prevalence rate has remained relatively stable over the past 40 years. Although PD risk is far greater in older subjects, patients with young onset are not that uncommon in the community, and health and social care provision should reflect their needs.

Previous epidemiological studies in the UK reported the crude prevalence of Parkinson's disease (PD) as 113–164 per 100 000 persons.[1–8] PD prevalence studies usually present data by current age and ignore age at disease onset. While young onset PD (YOPD) is rare, with an incidence of approximately 7 per million per year under the age of 50 years,[9] YOPD cases may be more common among all prevalent cases because of increased survival. We have completed a community based prevalence study of PD in Cardiff, South Wales, UK. The aim of this study was to specifically examine what proportion of prevalent cases had young onset disease, to study how age at onset influences source of health care and undertake a meta-analysis of all published UK prevalence studies to examine if there are geographical and temporal variations.

METHODS

We identified potential PD cases from primary care by undertaking two standardised searches using diagnostic Read Code F12 and sub-codes and any of the dopaminergic group of drugs used in PD (see appendix 1 online), excluding bromocriptine and amantadine because of their frequent use in conditions other than PD. After removing duplicates, a unique list of general practitioner case records were screened (MMW). Cases were defined as prevalent if they (a) were alive and symptomatic during the period January to December 2006, (b) were registered with a participating practice, (c) had been diagnosed as having PD and (d) met the Queen Square Brain Bank criteria[10] at clinic assessment or if the information held in the clinical notes were consistent with a diagnosis of PD and without recognised exclusion criteria. Patients were invited by the general practitioners after excluding any miscoded patients and those felt unsuitable for contact (eg, patients with a terminal illness). Participating patients completed questionnaires and attended a clinical assessment. Anonymised patient information was used to monitor recruitment and calculate prevalence rates. Notes were cross checked for each patient registered with the participating Cardiff general practices and attending the main secondary care PD Clinic in Cardiff over a 6 month period and where available from consultant neurologists in Cardiff using pseudo-identifiers. In addition, neurology consultants in Cardiff were asked to recruit patients who resided in Cardiff and whom had not yet been approached.

Crude prevalence rates and 95% confidence intervals (CI) were calculated using the Poisson distribution and standardised to the 1997 England and Wales population. Previous studies were reanalysed using the same standard population. We calculated the between study variation from a mixed effects Poisson model.

RESULTS

Forty-five out of 54 (88%) of the eligible primary care practices participated, providing a population denominator of 292 637 (96% of the Cardiff population). The diagnostic search yielded 731 unique potential cases (see web fig 1 online). A total of 378 cases were excluded (210 were prescribed dopaminergic agents for an alternative diagnosis, 96 cases had secondary parkinsonism, 72 patients did not have PD as either miscoded (26), essential tremor (35) or did not have their diagnosis revised after specialist review (11)).

We identified an additional 49 cases (20 from general neurology clinics, 27 from PD clinic, one

Table 1 Age, sex specific and standardised prevalence rates of Parkinson's disease

	Total			Men			Women		
Age (years)	PD cases	Population size	Age specific rates per 100 000	PD cases	Population size	Age specific rates per 100 000	PD cases	Population size	Age specific rates per 100 000
0–29	0	122 571	0	0	61 661	0	0	60 910	0
30–39	1	44 399	2.3	0	23 397	0	1	21 002	4.8
40–49	4	40 523	9.9	4	21 429	19	0	19 094	0
50–59	24	32 249	74	14	16 901	83	10	15 348	65
60–69	63	23 155	272	38	11 616	327	25	11 539	217
70–79	129	17 481	738	68	893	830	61	9288	657
>80	159	12 259	1297	74	413	1677	85	7846	1083
Crude rate per 100 000	380	292 637	130	198	147 610	134	182	145 027	126
Age standardised rates per 100 000*	142 (128, 156)			171 (147, 195)			120 (103, 138)		

*Rates were directly standardised to the England and Wales 1997 population.
PD, Parkinson's disease.

self-referral, one other), resulting in 402 potential cases. Fifteen cases were excluded before examination as not being PD. A total of 132 of the 387 potential prevalent cases were examined (35%) and seven additional cases (5%) were excluded as not PD. Only one diagnosis revised case had not seen a secondary care specialist. This resulted in 380 prevalent cases (182 females, 198 male).

Prevalence rates increased with age (see table 1) although males rates were greater at all ages. The age adjusted rates were 142 per 100 000 (95% CI 128 to 156 per 100 000) overall, and male and female rates were 171 (95% CI 147 to 195) and 120 (95% CI 103 to 138), respectively. The male to female prevalence rate ratio was 1.43 (95% CI 1.17 to 1.76; $p = 0.001$).

Age at symptom onset was obtained for 336 of the 380 (88%) prevalent patients (see web table 1 online). For men, mean age at onset was 67.7 years (95% CI 66.0 to 69.3 years) and for women mean age at onset was 69.7 years (95% CI 68.1 to 71.4 years). There was a bimodal distribution of age at onset with peaks at 40–44 years and 75–79 years. PD had begun in 3.6% of patients before the age of 45 years. The average disease duration for the prevalent group was 6.2 years. The YOPD group (onset <45 years) had longer disease duration (11.1 years, 95% CI 7.9 to 14.4 years) than the later onset (onset ≥45 years) PD group (6.0 years, 95% CI 5.4 to 6.5) with a significant difference of 5.1 years (95% CI 2.2 to 8.0; $p = 0.0006$). Cases who did not attend the clinic had an older age at onset but had the same duration of disease as those who did (see web table 2 online). In total, 85% of PD patients identified in primary care had been seen by a neurologist or PD specialist. Neurologists were most likely to have made the diagnosis of PD (44%). For YOPD, a neurologist made the diagnosis in 90% of cases ($p<0.001$) although in a substantial number of cases (31%) there was no information available. Overall follow-up care was mainly provided by the geriatrician led PD clinic (63%) and neurologists (17%) although, again, details were not available on follow-up care in 31%. Of those patients assessed in the research

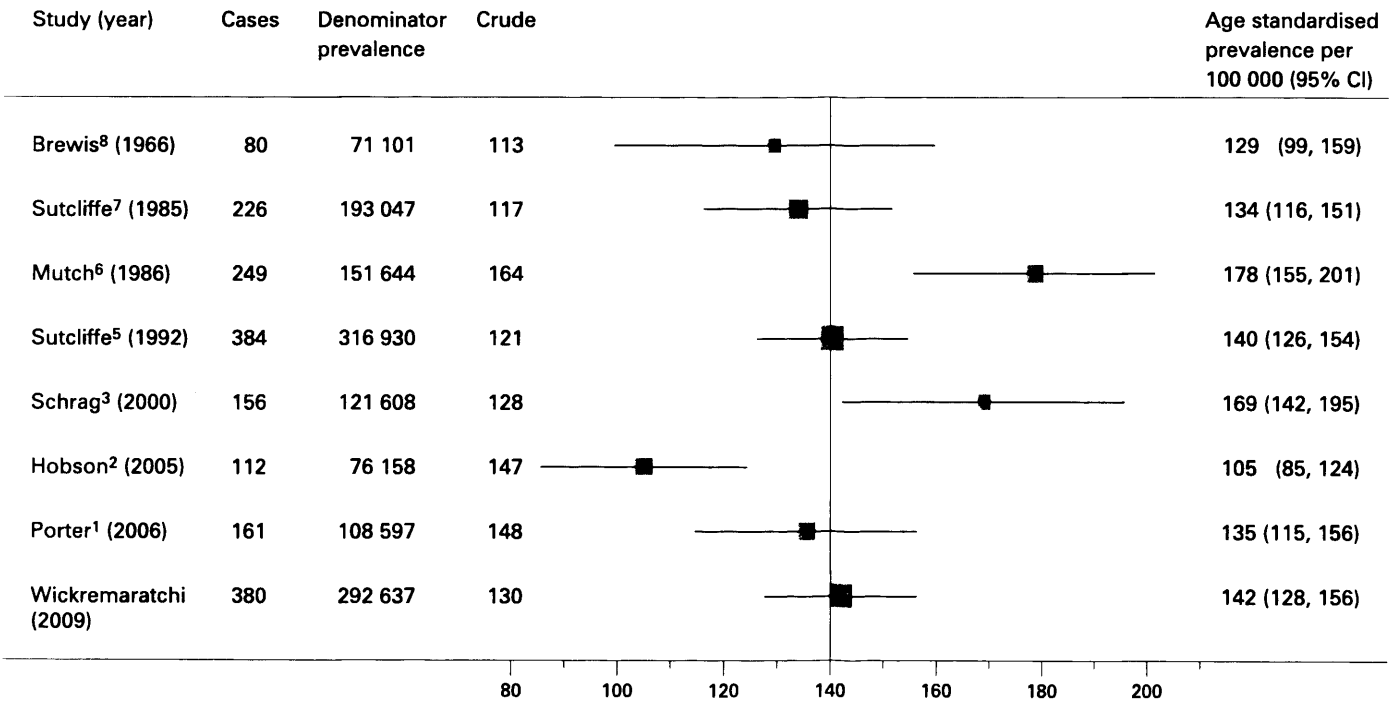

Figure 1 Forest plot of age standardised Parkinson's disease (PD) prevalence rates in the UK (1966–2008).

clinic, 45.5% were under follow-up by the movement disorder geriatrician, 22.7% by neurologists, 4.5% by general practitioners and 2.3% by other consultants.

Our prevalence rate (142 per 100 000) was very close to the global average for all previous UK prevalence studies (fig 1) but there was evidence of statistical heterogeneity (p value = 0.0006). Prevalence rates showed no systematic temporal change over the past 42 years.

DISCUSSION

We found that the prevalence of PD in Cardiff is similar to other studies in the UK (at approximately 140 per 100 000). Although the prevalence of young PD cases is much lower than that for older cases, 5.4% and 31.2% of the total prevalent PD population have their disease onset before 50 years or 65 years of age, respectively. Approximately 1 in 20 PD patients develop disease before the age of 45 years, normally considered to be a cut-off at which genetic autosomal recessive PD should be considered. While the crude rate of PD in those under 50 years in Cardiff is 2.4 per 100 000, the prevalence of those whose disease started before the age of 50 years is greater at 6.2 per 100 000. These figures equate to approximately 3700 people in the UK currently alive with YOPD and means that YOPD, defined by an age of onset below 50 years, is at least as common as motor neuron disease, Huntington disease and progressive supranuclear palsy.

Our meta-analysis of all UK studies suggests that the prevalence of PD in the UK is fairly uniform and has been relatively stable over the past 40 years. This is somewhat surprising given the increase in overall life expectancy, increased awareness and better management of PD, which would if anything increase prevalence. It is possible that incidence has declined but the incidence trends from 1976 to 1990 from Rochester, Minnesota, were relatively stable.[11] More recent studies are likely to have excluded other parkinsonian conditions, such as multiple system atrophy (approximately 10% of cases),[12] which may have been misdiagnosed as PD in the past.

We believe that the heterogeneity between studies can be explained by methodological differences. The study from Aberdeen actively searched for cases in nursing homes, which would have an over-representation of PD cases.[6] In contrast, the study from rural Wales[5] did not use diagnostic databases but relied on prescription records and referrals. In addition, it is not known whether PD survival is worse in rural compared with urban areas.

Almost all of the YOPD patients were diagnosed by a neurologist but only one-third of the later onset patients. Recent national guidelines[13] suggest that the diagnosis of PD should always be made by a specialist but this was not always the case at the time of our study.

Neurologists only looked after about half of the YOPD patients, and few (9%) of those whose disease started after the age of 65 years. A substantial minority (15%) of PD patients were followed-up solely by their general practitioners.

Limitations

Although we obtained a very high rate of participation from our primary care practices in Cardiff, we only clinically examined about one-third of all the cases, and older cases were less likely to be seen. We also did not invite cases with a diagnosis of essential tremor although the previous London study[3] identified patients with unrecognised tremor dominant PD. In that study, 11 of the 56 patients with non-parkinsonian tremor had probable or possible PD and their inclusion increased the number of PD cases by 7.9%.[14]

In conclusion, our prevalence estimate suggests that rates have remained relatively constant over the past 40 years. Although PD is a disease of the elderly, YOPD is far more common than appreciated, and the provision of health and social care for these patients should be an important consideration.

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REFERENCES

1. **Porter B,** Macfarlane R, Unwin N, *et al*. The prevalence of Parkinson's disease in an area of North Tyneside in the North-East of England. *Neuroepidemiology* 2006;**26**:156–61.
2. **Hobson P,** Gallacher J, Meara J. Cross-sectional survey of Parkinson's disease and parkinsonism in a rural area of the United Kingdom. *Mov Disord* 2005;**20**:995–8.
3. **Schrag A,** Ben-Shlomo Y, Quinn NP. Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. *BMJ* 2000;**321**:21–2.
4. **MacDonald BK,** Cockerell OC, Sander JW, *et al*. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;**123**:665–76.
5. **Sutcliffe RL,** Meara JR. Parkinson's disease epidemiology in the Northampton District, England, 1992. *Acta Neurol Scand* 1995;**92**:443–50.
6. **Mutch WJ,** Dingwall-Fordyce I, Downie AW, *et al*. Parkinson's disease in a Scottish city. *BMJ (Clin Res Ed)* 1986;**292**:534–6.
7. **Sutcliffe RL,** Prior R, Mawby B, *et al*. Parkinson's disease in the district of the Northampton Health Authority, United Kingdom. A study of prevalence and disability. *Acta Neurol Scand* 1985;**72**:363–79.
8. **Brewis M,** Poskanzer DC, Rolland C, *et al*. Neurological disease in an English city. *Acta Neurol Scand* 1966;**42**(Suppl 24):1–89.
9. **Van Den Eeden SK,** Tanner CM, Bernstein AL, *et al*. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol* 2003;**157**:1015–22.
10. **Litvan I,** Bhatia KP, Burn DJ, *et al*. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* 2003;**18**:467–86.
11. **Rocca WA,** Bower JH, McDonnell SK, *et al*. Time trends in the incidence of parkinsonism in Olmsted County, Minnesota. *Neurology* 2001;**57**:462–7.
12. **Schrag A,** Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet* 1999;**354**:1771–5.
13. **Royal College of Physicians.** National Collaborating Centre for Chronic Conditions. *Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians, 2006.
14. **Schrag A,** Ben-Shlomo Y, Quinn N. How valid is the clinical diagnosis of Parkinson's disease in the community? *J Neurol Neurosurg Psychiatry* 2002;**73**:529–34.