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Title page

The estimated life expectancy in a community cohort of Parkinson's disease patients with and without dementia, compared to the United Kingdom population.

Peter Hobson, Jolyon Meara, Lianna Ishihara-Paul[2].

Academic Unit (North Wales)
Cardiff University
Glan Clwyd Hospital
Rhyl LL18 5UJ

Email: peterhobson@hotmail.com

[2] Dept Worldwide Epidemiology, GlaxoSmithKline Pharmaceuticals, Harlow, UK

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Abstract

Objective: To compare survival, life expectancies (LE), and the anticipated age at the time of death (AAD), in a community-based cohort of Parkinson's disease (PD) patients with and without significant cognitive impairment, with an age sex matched population of England and Wales.
Methods: The age and sex specific standardised mortality ratios (SMR) were calculated and stratified by dementia status. The LE and AAD estimations were calculated from the SMR's of the 2003 United Kingdom population, using a modified Gompertz function.
Results: In total, 166 PD patients participated in the investigation, of which 91 died by the four-year follow-up. The overall SMR was 2.09 (95% CI 1.68, 2.57). Demented patients had significantly higher SMR's than non-demented patients (SMR3.10, 95% CI 2.39-3.96 vs. SMR 1.15, 95% CI 0.75 – 1.69 $p< 0.001$. In our cohort, the LE in younger onset demented patients (55-74 years) was much lower than in non-demented patients (7.5; SD 3 vs. 12.4; SD 7). Likewise, the estimated AAD in younger onset patients with dementia was also much lower (demented 72.4; SD 4 vs. not demented 77.8; SD 7). In older onset patients with dementia (< 75 years), the differences in LE (demented 2.1; SD 1 vs. not demented 4.7; SD 4), and AAD were less apparent (demented 89.5; SD 6 vs. not demented 92.2; SD 6).
Conclusion: The survival, LE and AAD in patients with PD is much lower compared with the general population, apart from those patients who do not develop dementia, who appear to have near normal population mortality rates. However, dementia and younger onset of PD appear to be important determinants of survival, LE and AAD.

Introduction

Within the next quarter century as a result of increasing life expectancy world wide, there will be at least 9.3 million individuals aged over 50 with a diagnosis of Parkinson's disease (PD).[1] Although the motor features of PD are the most obvious initial manifestations of this disorder, with disease progression, non-motor symptoms, and in particular dementia, become the most life threatening, disabling and challenging symptoms to manage.[2] The prevalence of dementia is strongly linked to age and community based studies have suggested that the risk of dementia in older subjects with PD is between five to six times that of an age matched population without PD. [3,4] A recent follow-up of a PD cohort in Australia at 20-years reported that 83% of its survivors were demented.[5] The extent to which non motor features of PD such as dementia influence survival remains unresolved.

In the pre-levodopa treatment era, mortality rates for PD were reported of between 1.6 to 2.9 times higher than the general population. [6-8] Following the introduction of levodopa, mortality in PD appeared to decline and this was attributed to more effective antiparkinsonian treatments. [9-17] However, a large proportion of these studies were methodologically flawed and did not control for non-motor symptoms associated with PD.[18] More recent community based and clinical investigations have reported mortality rates ranging from normal life expectancy to over twice that of the general population (Table1).[19-29] Several investigations have suggested that both incident and prevalent dementia are predictive for increased mortality in PD. [5,20,23-25,30,32] However, such estimates, because of differing methodologies applied, the inclusion of mixed heterogeneous cases of parkinsonism, and because few investigations have employed community or population based sample designs, the magnitude of this increase is still uncertain**.** Furthermore, most investigations have simply reported mortality rates rather than estimated life expectancy, which in recent investigations appear to describe better the interaction between survival and disease. [28,32,33] In the post-levodopa era, it remains unclear if survival in PD differs substantially from that of a normal population and how age-related mortality rates are influenced by dementia.

The aim of this study was to compare survival in a community-based cohort of PD cases with and without dementia at baseline with an age sex matched population of England and Wales. We also investigated the associations with prevalent and incident dementia in the cohort of patients, controlling for disease specific and non-motor variables. We also calculated life expectancies (LE; anticipated mean remaining time to live) based on standard mortality rates (SMR), to compare the LE and the anticipated age at the time of death (AAD) of the PD patients by age group, gender, and the presence or absence of dementia, compared to the general population of England and Wales

Table 1. Population and community investigations from 2000-2008

Berger *et al* 2000[19]	RR	2.3	(95% CI, 1.8-3.0) †
Levy *et al* 2002[20]	RR	2.2	(95% CI, 1.1-4.5) ††
Elbaz *et al* 2003[21]	RR	1.6	(95% CI, 1.2-2.1)
Fall *et al* 2003[22]	CMR	1.6	(95% CI, 1.3-1.8)
Herlofson *et al* 2004[23]	SMR	1.35	(95% CI, 1.05-1.7)
Hughes *et al* 2004[24]	HR	1.64	(95% CI, 1.2-2.2) †††
De Lau et al 2005[25]	HR	1.83	(95% CI, 1.5-2.3)
D'Amelio *et al* 2006[26]	OR	2.1	(95% CI, 1.4-3.1)
Chen *et al* 2006[27]	RR	1.6	(95% CI, 1.3-2.0) ††††
Driver *et al* 2008[28]	HR	2.3	(95% CI, 1.8-2.9) ††††
Diem-Zangerl *et al* 2009[29]	SMR	1.3	(95% CI, 1.1-1.5) †††

† Data derived from pooled data sets; †† Not standardised to index population; ††† Clinical population; †††† single gender investigation.
RR = Relative Risk; CMR = Cumulative mortality incidence ratio SMR = Standard mortality ratio; HR = Hazard ratio; OR= Odds ratio.

Methods

Patients and methods.

The patient recruitment methodology of this investigation has been previously reported.[4,34] Briefly, cases of possible PD were ascertained from 74 general practices in a geographically defined area in North Wales. Four hundred and two possible cases were identified of whom 213 fulfilled PD Brain Bank clinical diagnostic criteria for probable PD.[35] At study entry, 166/213 were assessed and reasons for non-participation are described elsewhere. All patients were assessed with the Hoehn and Yahr scale,[6] the Webster scale,[36] the UPDRS motor subsection,[37] the 15-item GDS,[38] the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG),[39] the Parkinson's disease Activities of Daily Living Scale (PADL)[40] and the EuroQol 5D (EQ-5D) health related quality of life measure.[41] Demographic variables were recorded which included age, gender, educational attainment, social class, onset age of PD diagnosis, and the duration of PD symptoms. Patients were also asked to subjectively rate their response to their antiparkinsonian medication. The diagnosis of dementia was based upon neuropsychological assessment, patient, and carer/informant interviews, along with the application of the Diagnostic and Statistical Manual of Mental disorders fourth edition criteria.[42] At study entry, 86/166 of the cohort were not considered demented, which has previously been reported. The study period was 4 years, from January 1, 1997 to December 31, 2000. The local research ethics committee approved this study.

Statistical analysis

Descriptive statistics (mean, SD, median) were used for continuous variables, whereas categorical variables were described as percentages of subjects in each group. Student *t*-tests, the chi-square test, and Univariate log-rank statistics were employed to examine between group differences and between observed and expected survival curves (all values 2-tailed, $p < 0.05$). The survival time of subjects was calculated from the date of baseline examination. Reasons for censorship included loss to follow-up and refusal. In these circumstances, the date of censoring was assigned to the midpoint of the corresponding follow-up interval. The Kaplan-Meier estimates were used to calculate the observed survival curves. Cox proportional hazard analysis was employed to investigate if one or more covariates were related to mortality. Cox proportional hazards and Cox time-dependent models were used for the multivariate analysis.

The age- and sex-specific standardised mortality ratios (SMR) were calculated, stratified by dementia status, by dividing the observed number of deaths in each group by the expected number of deaths in each group. The expected numbers of deaths were calculated using the age- and sex-specific Office of National Statistics (ONS) 2003 mortality rates multiplied by the person-time from each group in the study.

Estimated life expectancy (LE) can be calculated from the SMR using a modified Gompertz function.[43-46] The Gompertz equation is based on the observation that mortality rate tends to increase exponentially with age. Equation 1: $\mu_x = B \cdot e^{kx}$ is the mortality rate at age x; log (B) (y-intercept) and k (slope) are constants from the plot of natural log μ_x against x. Equation 2: SMR= ${}_1\mu_x / {}_0\mu_x$ and ${}_1\mu_x = \text{SMR} \cdot B \cdot e^{kx}$. ${}_1\mu_x$ is the age-specific mortality rate for the study population; ${}_0\mu_x$ is the age-specific mortality rate for the standard population. Equation 3: $e_x = [\ln (1 + k/ \mu_x) - 0.5 (1 + \mu_x/k)^{-2}] /k$. e_x is total remaining LE. The constants, B and k were calculated from the age- and sex-specific mortality rates for England and Wales in 2003 from the ONS. The inverse log of y-intercepts log (B) (males=0.0000320; females=0.0000142) and slopes k (males=0.095; females=0.103) were calculated from the graph of the natural log of the mortality rate against age. The assumption is that the 2003 mortality rates in England and Wales are similar to the present mortality rates, as these are the most recent available. Remaining LEs for men and women with PD were calculated separately by using Equation 2 and substituting the calculated mortality rate into Equation 3.

Using the SMR per group from the study produced the calculated remaining LE of PD patients. The anticipated average age at the time of death (AAD) was calculated by summing the average current age in each group and the average LE for that group (e.g. for men aged 55-59 in the general population the average AAD was 81.8 years, and for those with PD and dementia the AAD was 57.5 + 9.5 = 67.0 years).

Results

At baseline on January 1st 1997, 166 patients with PD were identified. During the 4-year follow-up, 91 patients (38 females, 53 males) died. The median survival time from onset of disease to death, was 9 years (95% CI, 7, 11). Descriptive data of the survivors and non-survivors of the cohort are presented in Table 2. Patients who died were significantly older ($p < 0.0001$), had an older onset of PD symptoms ($p < 0.0001$), more advanced disease ($p < 0.0001$), poorer response to antiparkinsonian medication ($p < 0.007$), poorer HRQoL (EQ-5D,$p < 0.05$),) worse ADL score (PADL, $p < 0.0001$), were more likely to be in institutional care ($p < 0.01$) and demented at baseline ($p < 0.0001$).

Overall univariate analysis of the cohort at baseline revealed that older age, later onset of PD symptoms, a worse response to PD therapy, greater disease severity (UPDRS), institutional placement, dementia, worsening HRQoL and ADL, were all significantly associated with mortality (Table 3). These variables were entered into the multivariate Cox model, where all of the variables associated with mortality could be removed apart from age 1.09 (95% CI 1.03-1.10) and prevalent dementia 2.7 (95% CI 1.56-4.67). Controlling for prevalent cases of dementia at baseline in a time dependent Cox model revealed that incident dementia (1.9, 95% CI 1.36-2.7), increasing age (1.08, 95% CI 1.03-1.16) and increasing UPDRS total motor scores (1.09, 95% CI 1.03-1.15) were associated with increased mortality.

Table 2. Demographic and clinical characteristics, and between group differences of the PD cohort

	Alive	Dead	*p* Value
Age	74.9(8.3)	77.8 (7.1)	0.02
Sex			
Female	37	38	
Male	38	53	0.33
Duration of symptoms	7.5 (7.1)	8.7 (6.6)	0.0001
GDS	4.2 (2.7)	5.4 (3.1)	0.01
H & Y	2.7 (0.7)	3.5 (0.8)	0.0001
Webster	15.1 (4.5)	17.2 (4.8)	0.004
UPDRS-motor	22.3 (11.9)	32.5 (13.2)	0.0001
CAMCOG	82.2 (19.2)	73.9 (16.8)	0.01
EQ-5D	0.79 (4.1)	0.43 (3.2)	0.04
PADL	2.6 (1.1)	3.3 (1.0)	0.0001

GDS-15 = shortened Geriatric Depression Scale; H & Y = Hoehn & Yahr scale; UPDRS-motor = Unified Parkinson's disease rating scale motor subscale; CAMCOG =Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG), EQ5-D = EuroQol HRQoL assessment; PADL = Parkinson's Activities of Daily Living Scale;
Student t-test, Chi square for comparisons, 2-tailed *p*-values

Table 3.

Baseline Univariate models of association with mortality at baseline

Variable	Log-rank statistic
Age	23.3***
Age at onset of PD	4.6*
Hoehn & Yahr scale	10.3*
Webster scale	6.9*
UPDRS (motor)	11.7**
Response to therapy	7.1*
Dementia	42.8***
Institutional placement	14.2**
EQ-5D	9.5**
PADL	6.3*
GDS-15	2.8
Gender	1.4
Educational attainment	3.6
Social Class	0.05

** p < 0.05; ** p < 0.001; *** p< 0.0001*
UPDRS = Unified Parkinson's disease rating scale; EQ5-D = EuroQol HRQoL assessment;
PADL = Parkinson's Activities of Daily Living Scale; GDS-15 = shortened Geriatric Depression Scale

The SMR for the whole cohort (n=166) was 2.09 (95% CI 1.68-2.57) times higher than the comparable age and sex distribution of the England and Wales population (Table 4). The survival curve for the whole PD cohort is shown in Figure 1. Both men and women in the cohort had a higher than expected SMR (Female 2.11, 95% CI 1.49-2.90; Male 1.95, 95% CI 1.46-2.55). Dichotomising patients into younger onset < 75 years, and older onset ≥ 75 years, revealed SMR's of 5.62 (95% CI 3.78–8.04) and 2.75 (95% CI 2.09-3.53) respectively. Patients who were demented at baseline (n = 80) had a significantly higher SMR than non-demented patients (SMR 3.10 95% CI 2.39-3.96 vs. SMR 1.15, 95% CI 0.75-1.69 p< 0.001 see Figure 2). Controlling at baseline for prevalent cases of dementia, and including incident cases only, the SMR of the patient group (SMR 2.37, 95% CI, 1.31-3.75) was still found to be much higher than the comparable general population.

Table 4: Standard mortality ratios of the Parkinson's disease cohort (SMR).

Total	N	Observed Deaths	SMR	95% CI
Total	166	91	2.09	1.68-2.57
Sex				
Female	75	38	2.11	1.49-2.90
Male	91	53	1.95	1.46-2.55
Cognitive function				
Demented	80	65	3.10	2.39-3.96
Non-demented	86	26	1.15	0.75-1.69

Figure 1:

Figure 2:

Mean life expectancy:

We employed the Gompertz function calculations and the 2003 UK mortality rates to estimate the LE of our PD cohort compared with the general population employing the SMR's calculated from our data, stratified by age, sex and cognitive function (non demented/demented). The LE and AAD of the non demented/demented patients are shown in Table 5. Comparisons of the LE and AAD of non demented/demented patients and the general UK population are shown in Figures 3 and 4. Overall, PD patients had a lower LE and shorter AAD compared to the general population especially in the presence of dementia. Male patients had a shorter LE and lower AAD compared to female patients.
Younger patients with and without dementia had a lower AAD compared to the general population. To explore these differences, the patient group was dichotomised into younger onset (55-74 years) and older onset (≥ 75 years) groups. Between the ages of 55-74 the average LE for the demented group was 7.5 (SD 3) and 12.4 (SD 7) years in the non-demented group dementia compared to a LE of 19.8 (SD 5) years in the general population. The AAD in the younger onset demented group was 72.5 (SD 4), and 77.8 (SD 7) in the non-demented group, compared to a general population AAD of 84.8 (SD 2). In the older onset group, patients with dementia had a LE of 2-years (SD 1), compared with an LE of 4.7(SD 3) years in the non-demented group, and an LE of 6.2 (SD 3) years in the general population. The AAD was 89.5 (SD 6) years in the demented group, 92.2 (SD 6) years in the dementia free group, and 93.7 (SD 5) years in the general population.

Table 5: Decrease in life expectancy remaining for Parkinson's disease patients with and without dementia, compared to the general population stratified by age and sex, employing the Gompertz function and 2003 UK mortality rates.

Age Range	*LE dementia free		**AAD dementia free		*LE demented		**AAD demented		*LE General population		**AAD in 2003 general UK population	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
55-59	10.1	24.0	67.6	81.5	9.5	12.5	67.0	70.0	24.4	27.8	81.9	85.3
60-64	7.5	19.8	70.0	82.3	7.0	9.6	69.5	72.1	20.3	23.4	82.8	85.9
65-69	5.6	15.9	73.1	83.4	5.2	7.3	72.7	74.8	16.4	19.2	83.9	86.7
70-74	3.9	12.4	76.4	84.9	3.6	5.4	76.1	77.9	12.9	15.3	85.4	87.8
75-79	4.5	11.0	82.0	88.5	2.8	4.3	80.3	81.8	9.8	11.7	87.3	89.2
80-84	3.1	8.1	85.6	90.6	1.8	2.9	84.3	85.4	7.2	8.7	89.7	91.2
85-89	3.2	6.1	90.1	93.6	1.7	2.3	89.2	89.8	5.2	6.1	92.7	93.6
90-94	2.3	4.2	94.8	96.7	1.1	1.4	93.6	93.9	3.7	4.3	96.2	96.8
95+	1.6	3.0	99.1	100.5	0.8	1.0	98.3	98.5	2.8	3.0	100.3	100.5

** LE = Life Expectancy; **AAD = Anticipated age at time of death.*

Figures 3 & 4

Discussion.

This is the first investigation to our knowledge to report the SMR's, estimated Life expectancy (LE) and the average age of death (AAD) in a community cohort of PD patients stratified by cognitive status, compared with the England and Wales general population. The overall mortality rate in our cohort was over twice the expected rate in the general population, which is comparable to recent community based investigations, where the overall increased risks for mortality in PD was reported to be between 1.35 and 2.01. [21, 23, 24] Furthermore we established that the mortality rate in younger onset patients was higher than older onset patients, compared to the general population.
In our cohort, the risk of death was strongly related to the presence of dementia, as there was a three-fold increase in the SMR in the demented group. When adjustment was made for prevalent cases of dementia at baseline, the SMR fell to 1.15**,** which is close to the general England and Wales population mortality rates. This is in agreement with reports from recent community and population based investigations. [19-30] Our findings are also consistent with previous investigations demonstrating an increased risk of mortality in PD patients with dementia and cognitive impairment.[47-51] However, case ascertainment and population recruitment bias in these earlier investigations often make it difficult to establish if the association between PD dementia and mortality might have arisen through sampling error. Two recent investigations have reported around a two fold increased risk of mortality in both incident[20] and prevalent dementia. [24] However, the former investigation did not have a comparable reference group, and the latter drew the PD cohort from a clinical population alone and did not control for incident cases of dementia. The age structure and high baseline prevalence of dementia is likely to account for the significant mortality in our cohort. When we adjusted for incident cases of dementia in our cohort, the SMR was 2.37**,** which is similar to other community based investigations in Norway,[23] and the Netherlands,[25] where mortality risks of between 1.61 and 2.85 for cases with cognitive `impairment or dementia, have been reported. The lower mortality risk reported in the Norwegian study (SMR 1.61) may have arisen because they included all cases of parkinsonism and dichotomised neuropsychological screening scores alone, to determine if a patient had cognitive impairment, rather than employing neuropsychological assessment and application of DSM-IV criteria for the development of dementia.
This investigation also confirmed that overall LE and AAD in patients with PD is lower than the general population, particularly in younger onset patients and those with dementia. Our findings are comparable to those recently reported in a UK investigation [27] using the Gompertz calculations for mortality in PD, where younger onset patients compared to older onset patients and the general population had a much reduced LE and AAD. A recent Norwegian investigation[21] explored the relationship with dementia and survival in PD, also reported a decreased total LE in demented patients and in male patients. Interestingly, female PD patients not only had a greater LE, but they also survived longer with dementia if they developed it.

Comparing mortality rates between pharmacological trials [52-55]and community populations is difficult because of the differing inclusion criteria for entry into these studies. Patients entered into pharmaceutical trials are likely to be fitter and younger than would be expected in a typical PD population. The results from the pooled data in the DATATOP cohort [53] for example, reported almost no differences in mortality rates (SMR 1.04), whereas Hely et al's longitudinal investigation, reported consistently higher SMR's (1.58,[50] 1.86, [28] 2.5[3]) in their cohort at 10,15 and 20 years. Despite the methodological differences between clinical trial and community based investigations life

expectancy in PD does appear to have increased in the post-levodopa era. However, a reduction in mortality rates is possibly due to not only better pharmacological management of PD, but also to the introduction of specialist managed services, multidisciplinary team interventions, and earlier identification of PD symptoms.

In conclusion, patients in our cohort who did not develop dement had a near normal survival rate. However, overall the average remaining life expectancy and average anticipated age at death in patients with PD are considerably reduced compared with the general population. In addition, the finding that the majority of this reduction is greatest in younger patients, and in patients with dementia, requires further exploration.

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Competing interests:
None declared

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Figure 1: Survival curve for the whole PD population

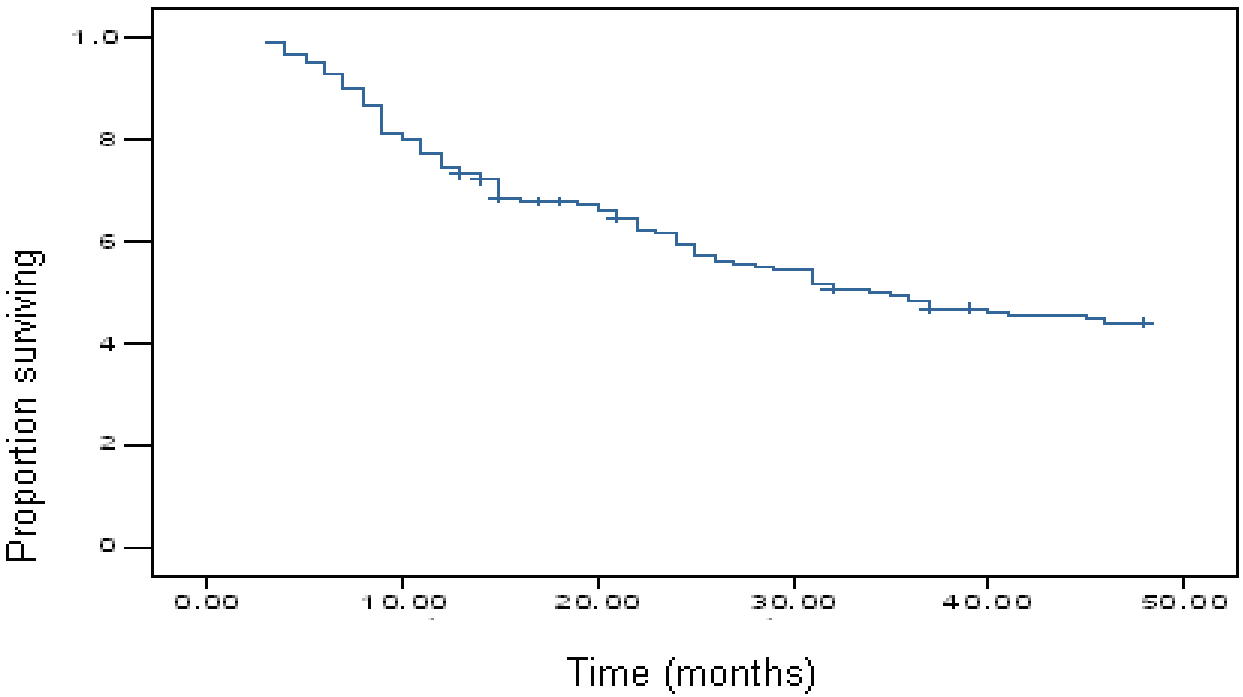

Figure 2:
Survival curves for the non demented (broken line) and demented patients

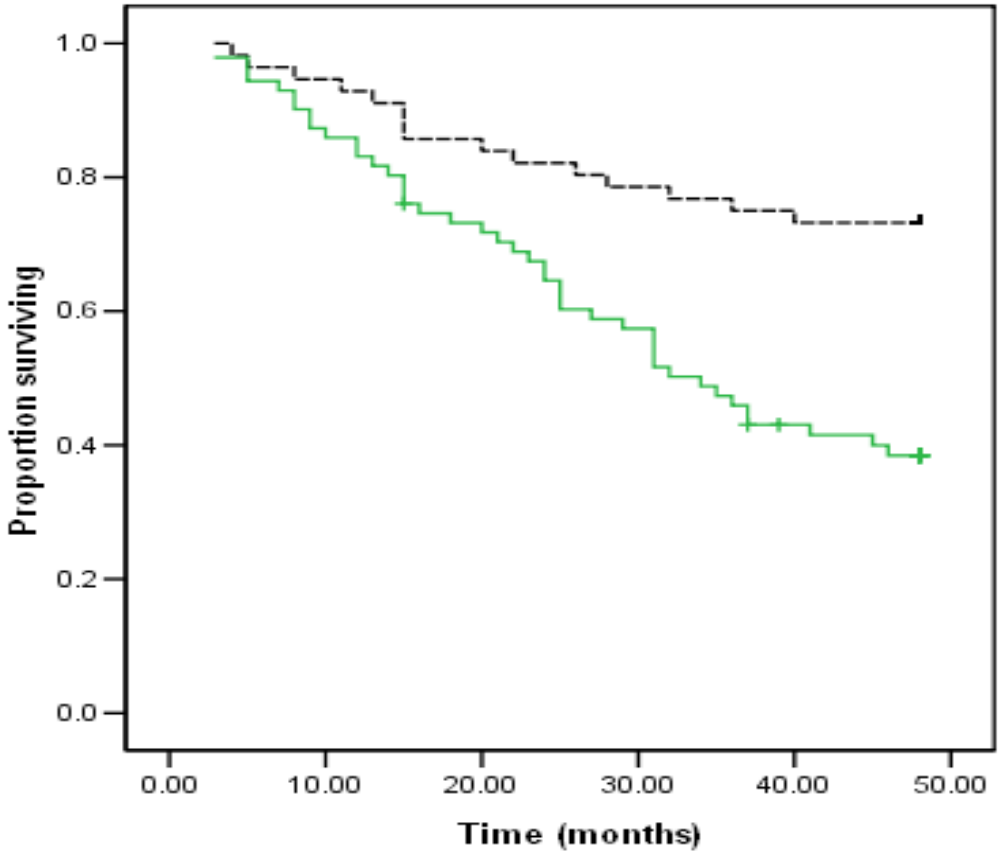

Figure 3: Average remaining life expectancies by age and sex for Parkinson's disease (dementia free/demented) patients and the 2003 UK population.

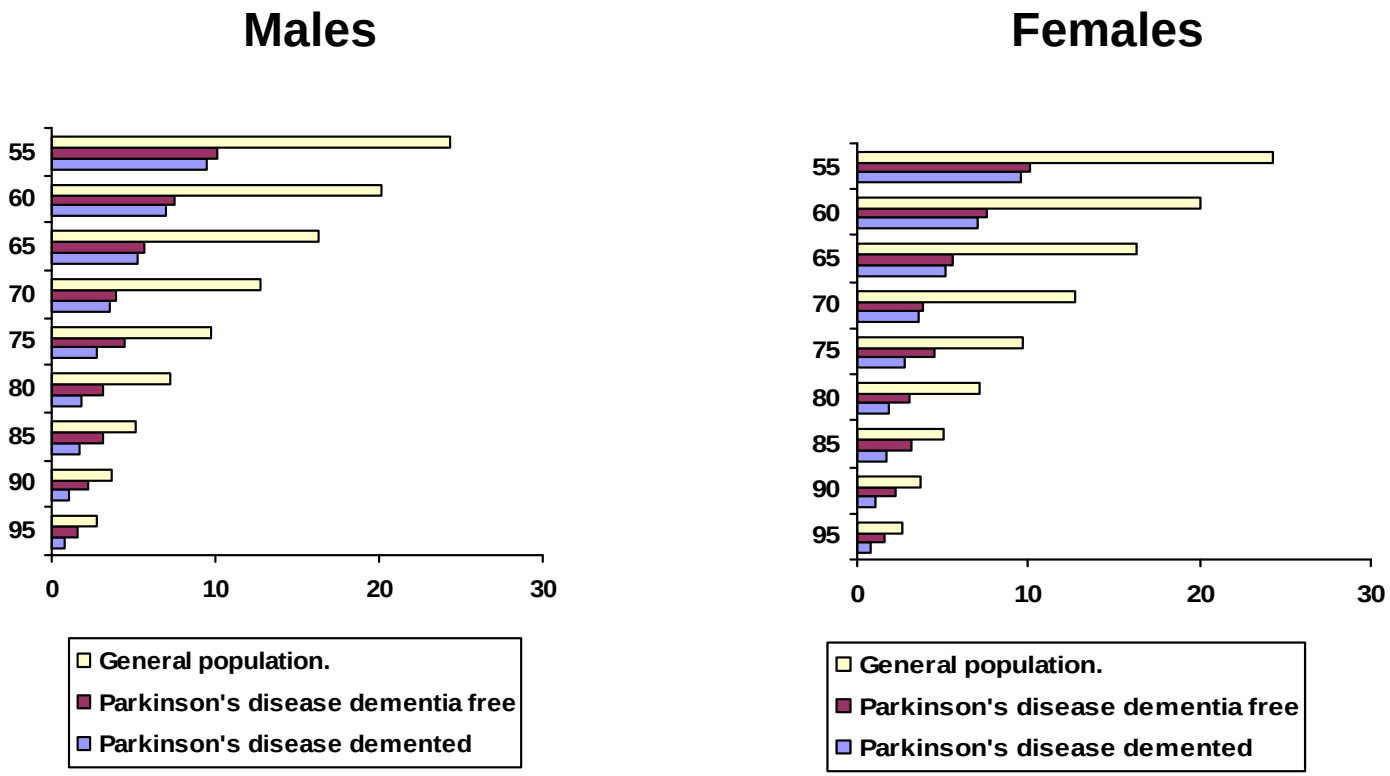
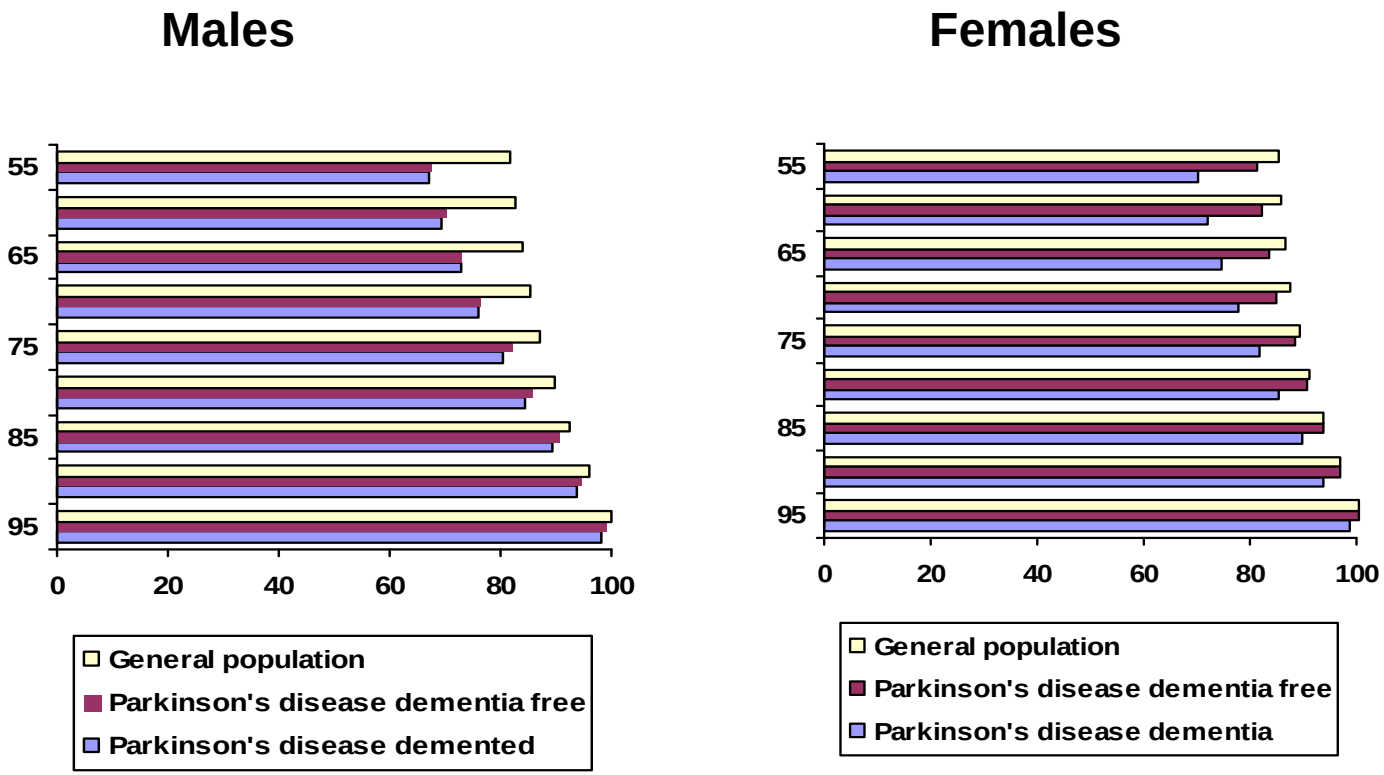
Figure 4: Average anticipated age at death for patients with Parkinson's disease (dementia free/demented) patients and the 2003 UK population.