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Mortality in the Denbighshire Parkinson's disease community cohort at 18-years.

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Abstract

Objective: To examine the reported causes of death in a community cohort of Parkinson's disease (PD) patients.
Setting and participants: A total of 166 PD patients and 102 controls were included in this investigation. Hospital and primary care records were employed to ascertain the number of individuals who died during the investigation period. The primary and underlying cause of death was extracted from certificates obtained from the United Kingdom General Register Office.
Results: There were 158 (95%) deaths in the PD and 34 (33%) deaths recorded in the control cohort. The Standard Mortality Rate (SMR) was 1.82 (95% CI: 1.55 – 2.13). Controlling for prevalent PD cases at baseline (n =80), the SMR was 1.72 (95% CI: 1.36 – 2.17), indicating that there was no excess mortality between the prevalent and incident cases ($p < 0.186$). The main cause of death reported in the PD cohort was pneumonia (52%), followed by cardiac related deaths (21%). PD as the primary or underlying cause was not reported in 75/158 (47%) of the cohort. In addition, although 144 of the cohort had a diagnosis of dementia, this was reported in less than 10% (n=14) of their death certificates.
Conclusion: This community based investigation established that PD is associated with a higher risk of mortality compared to the general population. In addition, we found that the majority of patients with PD if they survive long enough will develop dementia. However, the reporting of PD and dementia as a cause or underlying cause of death on certificates was found to be suboptimal. The results from this investigation suggest that use of mortality statistics alone in epidemiological studies, healthcare planning and provision need to be reconsidered, because they are not a valid or reliable source of data capture.

Strengths and limitations

- Community based longitudinal follow-up cohort design
- All patients fulfilled diagnostic criteria for Parkinson's disease and or dementia.
- Baseline and subsequent repeat measure data capture allowed analysis for predictive outcomes.
- Prevalent and incident cases of Parkinson's disease were included in the cohort, although this was controlled for in the analysis.
- Control cohort included subjects without known neurological condition and thus may have intruded bias in the outcome comparisons with the Parkinson's disease patients.

Introduction

Data drawn from death certificates is often employed by epidemiological, public health and research scientists to capture the incidence, prevalence and mortality in populations. In addition, these statistics are often utilized in the evaluation of public health interventions, setting priorities for medical research and health services, the planning of health services, and the clinical assessment of the effectiveness of those services. [1-3] The introduction of the revised International Classification of Diseases (ICD) system in 2001 aim was to improve the accuracy in the reported cause of death, where underlying conditions, mentioned in Part 1 or 2 of death certification take priority over others. [4,5] The underlying principle for this is that reporting of multiple causes of death should provide a better description of a particular disease or condition, allowing for more effective and meaningful data capture. The reliability of statistical information extracted from death certificates however still remains uncertain, where for example, rather than the underlying chronic condition being reported, a secondary cause of death is often reported as the main cause of death. [6-14]

Increasing elderly population demographic changes worldwide along with exponential rises in chronic conditions, will most likely place greater social and fiscal demands on existing clinical heath and social services. [15] To ensure that mortality and survival rates are more precisely captured for these chronic conditions, the relative contributions different diseases have upon survival and mortality need to be more accurately measured. The challenge is to ensure that more reliable data is recorded to allow for more efficient planning for healthcare services and clinical interventions. Parkinson's disease (PD) is a progressive neurodegenerative disease strongly associated with increased mortality and lower life expectancy than the general population. [16-28] In addition to the motor symptoms of PD, many patients often live with a significant number of other non-motor conditions which contribute to the symptomatology of the disease. [29-34] In particular, dementia occurs frequently in the elderly PD patient and has been shown to be a strong predictor for increased mortality. [25,35-45] This most probably has implications for the quality of death certification, which in previous investigations has been found to be inconsistent, under recorded or an inaccurate record of the cause of death in patients. [26,27,46-49] The methodological design of previous investigations, where cohorts have been drawn from clinical populations or pharmaceutical trails alone may partially explain the variability between studies.[50-52] Only a small number of investigations have employed prospective community study methods to ascertain the utility of death certification in PD, and furthermore few have included a comparison control group.

The aim of the present investigation is to examine the reported cause of death in a community cohort of PD patients and comparable group of individual's in the general population without neurological disease from the same geographical area. This will allow for exploration of the quality of death certification in these

individuals and to determine how often PD and or dementia is reported as a contributor to death in these individuals.

Methods

Patient and Control subjects

The PD Denbighshire cohort study provided data for analysis in the current investigation. [25,37,53] This cohort and the control cohort were drawn from a geographically defined area in North Wales United Kingdom (UK), and followed from 1997-2015. At study entry 166 patients all of whom met clinical criteria for probable PD were reviewed. [54] The causes of death were compared with a control cohort (n = 102) recruited from General Practitioner practices within the same geographical area from which the PD group was drawn. The control cohort were initially screened for possible signs of parkinsonism, Alzheimer's disease, history of a previous stroke, any other neurological or neurocognitive disorder, if they were found to have been treated with any psychoactive drugs, or a significant psychiatric, alcohol or substance abuse history. The included control subjects were matched for sex and of similar age to PD patients (± 3 years).

The PD cohort at study entry were assessed with the Hoehn and Yahr staging (H&Y), the UPDRS motor subsection, the 15-item Geriatric Depression Scale (GDS), the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG), the Parkinson's disease Activities of Daily Living Scale (PADL) and the EuroQol , health related quality of life (HRQoL) measure.[16,55-59] Demographic variables were recorded which included age, gender, educational attainment, social class, onset age of PD diagnosis, and the duration of PD symptoms. 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. [60]

Death certification collection and evaluation.

Review of hospital and primary care records were employed to ascertain the number of individuals who were deceased. All of the death certificates in this investigation were obtained from the local Births, Deaths, and Marriages central record office for the PD and control cohorts. Primary and underlying cause of death, along with the age of the subject and the age of death are recorded on all certificates in the UK. In addition, all certificates completed by a doctor within the UK and are coded using the ICD-10 system as follows:

Ia: Disease or condition leading directly to death.
I(b): Other disease or condition, if any, leading to I(a).
I(c): Other disease or condition, if any, leading to I(b)
II: Other significant conditions that contributing to death but not related to the disease or condition causing it.

From the information recorded on the death certificates, we grouped primary and underlying causes of death in to nine further categories which were, PD, Sepsis, Dementia, Cerebrovascular, Cardiac, Cancer, Pneumonia, Chronic lung disease, other disorders.

Statistics.

The age- and sex-specific standardised mortality ratios (SMR) were calculated for men and women 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 published UK age- and sex-specific Office of National Statistics (ONS).

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 logrank statistics were employed to examine between-group differences and between observed and expected survival curves (all values two-tailed, $p<0.05$). The survival time of subjects was calculated from the date of baseline examination. 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. All data were analysed with the SPSS statistical package version 19. [61] The relative risk (RR) and 95% confidence interval (CI) were calculated using the Altman formula and MedCalc software. [62,63]

Results

From baseline to the study end date (30/12/2015), 158/166 (96%) of the PD and 34/102 (33%) of the control cohorts were decedents. In Table 1 the demographic and clinical outcomes of the PD and control cohorts are shown. Figure 1 illustrates the Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts. The SMR for the whole PD cohort compared to the England & Wales 2013 population was 1.82 (95% CI: 1.55 – 2.13). Comparing prevalent and incident cases survival revealed an SMR of 1.72 (95% CI: 1.36 – 2.17), which indicated a non significant ($p < 0.186$) excess mortality between the groups (Figure 2). There were no statistical differences found between the PD and control cohorts age at death (PD cohort 80.7 (7.1), Control cohort 81.9(6.3); $z = 0.640$; $p > 0.552$). The strongest predictor for mortality in the PD cohort was the worsening motor symptoms (HR 1.06, $p< 0.01$). As a primary cause of death (Part 1a on UK death certificates), PD was recorded in just over 4% of the cohort. In sections 1b and 1c (conditions substantially contributing to death), PD was reported in 24% and 6% of cases respectively. In section II of the death certificates (co-morbid conditions substantially contributing to death); PD was reported in 19% of cases. Overall, PD as a contributing factor in the cause of death, was not reported

anywhere on 75/158 (47%) of the cohort certificates. The primary cause of death for the PD and control cohorts is shown in figures 3 & 4. The most common cause of death reported within the PD cohort (figure 2) was pneumonia (52%), followed by cardiac related deaths (21%). The most frequently recorded cause of death within the control cohort (figure 3) was cardiac disease (26%), cancer (24%), and pneumonia (18%). A comparison between the PD and Control cohorts revealed that the PD cohort were nearly three times more likely to have pneumonia recorded as a primary cause of death (RR, 2.94, 95% CI 1.40-6.19), Controlling for patients and controls with dementia still revealed a higher risk of mortality in PD for pneumonia (RR, 2.03, 95% CI 1.34-3.6). The controls compared to the PD cohort had over a threefold increased risk of having a cancer related disorder recorded as a primary or underlying cause of death (RR, 3.72, 95% CI 1.58 -8.72).

Disease progression within the PD cohort was significantly associated with a worsening HRQoL at death ($z = 4.5$; $p < 0.0001$). When compared to the controls, HRQoL was significantly poorer for the PD cohort ($z = 3.29$; $p < 0.001$). At the time of death, 83/158 (52%) of the PD and 9/34 (26%) of the control cohorts were living in institutional care ($z = 2.96$, $p < 0.003$). Overall, the PD cohort decedents had a threefold increased probability to be living in institutional care at death (RR 3.23, 95% CI 1.4-7.41). Controlling for age and duration of illness, the PD cohort living in institutional were also more likely to be demented (RR 2.7 (95% CI 1.21- 5.76). In contrast to the PD cohort, the control decedent's place of death was more likely to be in hospital (RR, 1.97, 1.48-2.62).

As a primary or underlying cause of death, dementia was underreported on both the PD and control certificates. Although 144/158 (91%) of the PD cohort had a diagnosis of dementia before their deaths, it was reported in only 14/144 of certificates. Similarly, only two of the control cohort had dementia recorded anywhere as a primary or underlying cause of death. Upon review however, a further four at the time of death had a confirmed diagnosis of dementia.

Discussion.

This investigation reports the cause of death recorded on the death certificates of PD and age matched control cohorts in Denbighshire in the UK. We have previously reported that the life expectancy and average age at death in this PD cohort is much lower than the general population. [25] In the current study the overall SMR for our PD cohort was 1.82, indicating an excess mortality, which remained even after controlling for prevalent cases of PD at baseline (SMR 1.72). This is similar to previous investigations where the SMR has been reported to range from 1.5 to 2.5. [22-26,28,49] However, recent community based incident cohort and incident clinical cohort investigations have reported lower SMR's of 1.29 (95% CI, 0.97-1.61), and 1.39 (95% CI, 1.10.-1.50), suggesting a moderate increase mortality compared to the general population. [28,64] The shorter duration of PD diagnosis, lower number of recorded deaths and shorter follow-up period compared with the current

investigation may partially explain these differences the current and previously reported UK investigation. In addition the Spanish investigation was limited by the retrospective analysis of a data set from 1978-1998 and recruitment solely from a clinical population.

Overall death certification and clinical research data appear to provide quite disparate mortality data in PD. Although our PD cohort had confirmed UKPDSBB criteria for probable PD, as a primary cause of death (Part 1a), it was recorded in just in over 4% of the cohort. A further 30% had PD recorded in parts 1b and c of their death certificates, and on Part II of certificates it was recorded in a further 19% of cases. Overall, PD was not cited anywhere on 47% of the death certificates, which falls approximately midway with previous certification studies of between 14–70%. [22,26,27,46-49] The disparity reported between studies is most likely evidence of the differing methodologies employed such as, populations drawn from pharmaceutical trials alone, clinical samples, or retrospective case or chart record analysis.

Pneumonia was the most cited primary cause of death (52%), with near a threefold higher increased risk compared to the controls, which has been frequently reported in other investigations. [22,26-30,38,64] Patients with PD, particularly as they become frailer with the progression of their illness, are at greater risk for pulmonary complications, due to obstructive ventilation dysfunction, upper airway dysfunction, and weakened strength of respiratory muscles. [65-68] The most frequently reported other causes of death were cardiovascular disease (21%), cerebrovascular disease (8%) and malignancy (6%).

This is the first study to our knowledge to describe underreporting of dementia as a primary, or underlying cause of death in a community based PD cohort. We have previously reported in this cohort the high prevalence of dementia of around 90%. [69] Upon review of the decedents death certificates, we found that less than 10% had any mention of dementia as an immediate or underlying cause of death. Previous general population investigations have also shown that rates of certification mentioning dementia as a main or underlying cause of death have been consistently under reported. [70-73] This perhaps is because certification tends to focus upon the immediate cause of death and does not really capture the multiple factors that contribute to death, particularly with elderly individuals with multiple co-morbidities.

This investigation found that the progression of PD motor severity, poorer HRQoL and dementia increased the likelihood of entering and residing in long term care before death. This may be a reflection of the duration, nature and the type of burden PD places upon relatives, especially those who have physical frailty themselves. Caring within the home setting may therefore become more impracticable and thus possibly precipitates entry into institutional care. The proportion of deaths in long term care amongst the PD cohort was also significantly higher than the control cohort. In contrast, the number of hospital deaths in the PD cohort was significantly lower than the control cohort (37% vs.

73%) and more patients died at home (other than a long care setting) compared to the controls (16% vs.12%). A recent study reported wide variations in the place of death of people with PD throughout the world, concluding that individual preference, social and socioeconomic circumstances; cultural, organisation and provision of health and palliative care all contribute to some extent the place of death. [74]

In common with previous mortality investigations we found fewer recorded cancer deaths within the PD cohort. [75] It is thought that mutations of the PARK2 (Parkin) gene found in 6-8% of PD patients may act in some cancers as a tumour suppressor proteins. [76] The absence or mutation of the Parkin gene is found in several tumour types, suggesting that the mechanisms of cell death in PD may play a role in the inhibition or formation of some cancers. [77] The decreased risk of mortality from cancer has also been reported in other neurodegenerative disease including Alzheimer's, Huntington's disease and in populations where mild to moderate with cognitive impairment has also been observed. [78-81 Further studies are needed to explore the associations, risks, possible genetic markers and underling mechanisms in PD and other neurodegenerative conditions, to improve and identify and understand the role of cell death and its decreased cancer risk.

We would caution the message often given to PD patients that they die with, rather than die of the condition. The non-motor features of PD such as dementia and autonomic dysfunction are frequently observed in all stages of the disease and most likely make a significant contribution to mortality.[82] A recent investigation reported that autonomic dysfunction and dementia in PD was predictive of increased mortality particularly in patients with orthostatic hypotension (OH).[83] Another meta-analysis which explored the association with OH and mortality in general populations also concluded that OH may confer a greater risk (RR, 1.40) for mortality. [84] The association between the non-motor features of PD disease and mortality needs further research to understand and determine if these are causal or not.

This study's strengths are the robust follow-up over an 18-year period of a community based cohort all of whom fulfilled criteria for PD and diagnostic re-evaluation was reviewed regularly over this period to ensure diagnostic accuracy. The repeat measure design of the study also allowed us to control for demographics, and motor and non-motor symptomatology. The limitations of the study are that the PD cohort had a mix of prevalent and incident cases, thus possibly over estimating the possible causal associations with mortality. However, controlling for prevalent and incident cases in our analysis did not reveal any between group significant differences. In light of our findings we feel that the current methods of capturing the cause of death significantly underestimate the true population burden of PD. The under reporting of dementia as an underling cause of death in this cohort in addition to PD, also suggests that the interpretation of and quality of mortality data currently is not a valid or reliable source of data. Furthermore we

would admonish the use of mortality statistics alone to plan for future service provision in this patient population.

Contributorship statement: PH and RJM conceived and designed the study, collected the data, and managed the database. PH managed the database, contributed to data cleaning, performed the statistical analyses. PH and RJM contributed to interpretation of the data. PH and RJM wrote the manuscript. All authors critically reviewed the manuscript and approved the final version to be published.

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Table 1:
Demographic and clinical outcomes of the PD and control cohorts

	Parkinson's disease	Control	*p< 0.05*
Gender (female %)	44%	41%	NS
Age at death	80.7 (7.1)	81.9 (6.3)	NS
Institutional care %	52%	30%	0.003
Place of death (Hospital)	37%	74%	0.002
EQ-5D (Weighted health)	0.58 (0.36)	0.79 (0.28)	0.001
EQ-5D (VAS %)	55 (16.5)	77 (17.6)	0.001
Onset of PD	67.3(10.7)	------	-----
Duration of PD	13.2 (8.8)	------	-----
UPDRS (motor section)	27.9(11.7)	------	-----
H & Y	2.9 (0.74)	------	-----
PADL	3.1 (1.1)	------	-----

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts

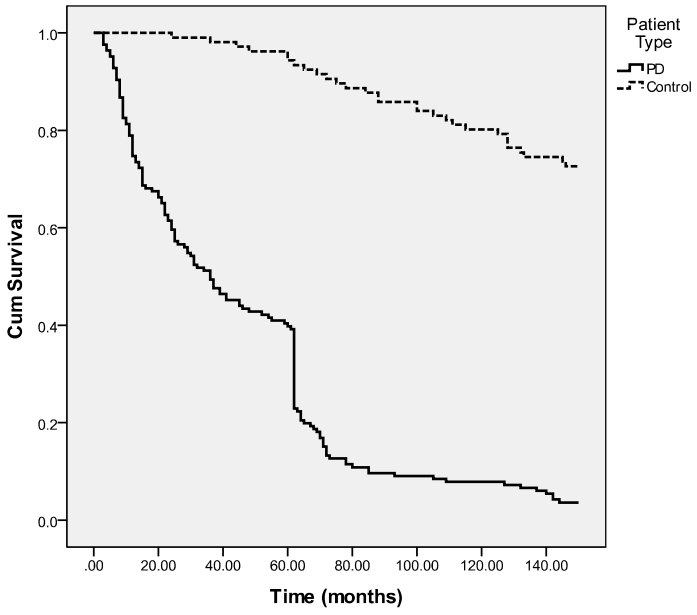


Figure 2: Survival curve analysis comparison between prevalent (n=76) and incident (n=80) PD cases.

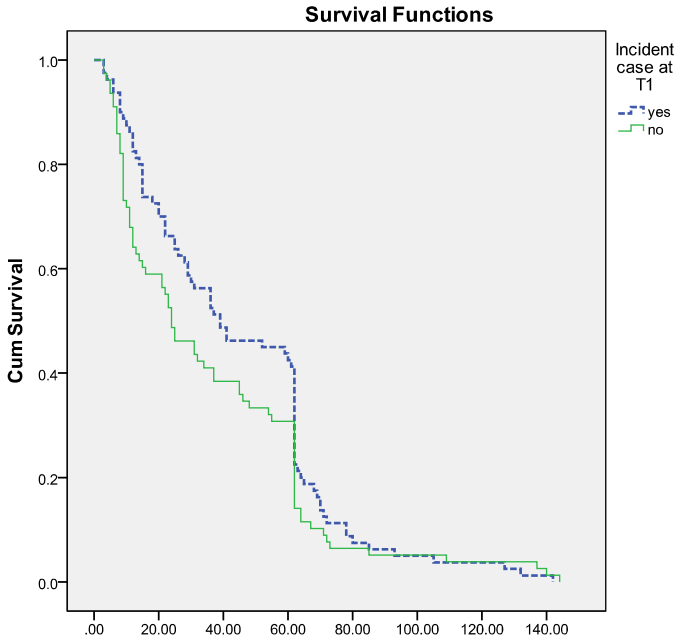


Figure 3: Primary cause of death reported for the PD cohort.

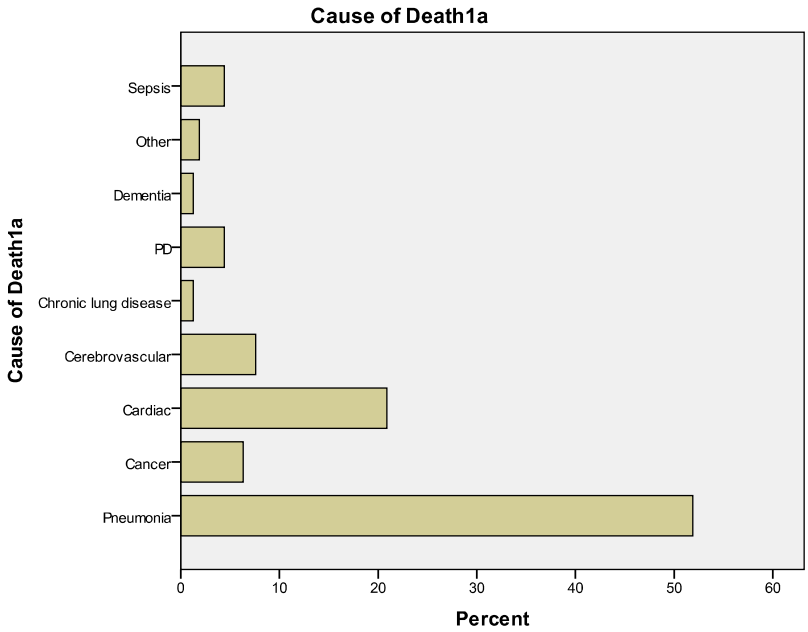
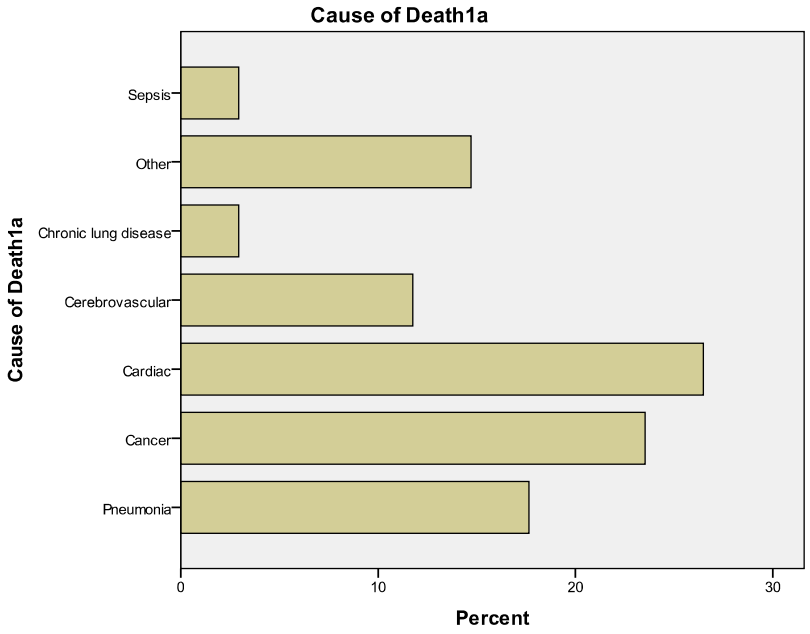


Figure 4: Primary cause of death reported for the control cohort.



STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,6,8
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5.6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	5,6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	5,6
		Cross-sectional study—Report numbers of outcome events or summary measures	--
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,6
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Mortality and the quality of death certification in cohort of Parkinson's disease and matched controls in North Wales United Kingdom at 18-years: a community based cohort study.

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Keywords:	Parkinson-s disease < NEUROLOGY, Mortality, Death certification, Dementia < NEUROLOGY

Mortality and the quality of death certification in cohort of Parkinson's disease and matched controls in North Wales United Kingdom at 18-years: a community based cohort study.

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Word count: 3213

Abstract

Objective: To estimate the survival, mortality and quality of death certification in a community cohort of Parkinson's disease (PD) patients and controls in North Wales United Kingdom (UK).
Setting and participants: A total of 166 PD patients and 102 controls were included in this investigation. Hospital and primary care records were employed to ascertain the number of individuals who died during the investigation period. The primary and underlying cause of death was extracted from certificates obtained from the UK General Register Office.
Results: There were 158 (95%) deaths in the PD and 34 (33%) deaths recorded in the control cohort. The Standard Mortality Rate (SMR) was 1.82 (95% CI: 1.55 – 2.13). The main cause of death reported in the PD cohort was pneumonia (53%), followed by cardiac related deaths (21%). PD as the primary or underlying cause was not reported in 75/158 (47%) of the cohort. In addition, although 144 of the cohort had a diagnosis of dementia, this was reported in less than 10% (n=14) of their death certificates.
Conclusion: This community based investigation established that PD is associated with a higher risk of mortality compared to the general population. In addition, we found that the majority of patients with PD if they survive long enough will develop dementia. However, the reporting of PD and dementia as a cause or underlying cause of death on certificates was found to be suboptimal. The results from this investigation suggest that use of mortality statistics derived from death certification alone in epidemiological studies, healthcare planning and provision need to be reconsidered, because they are not a valid or reliable source of data capture.

Strengths and limitations

- Community based longitudinal follow-up cohort design.
- All patients fulfilled diagnostic criteria for Parkinson's disease and or dementia.
- Baseline and subsequent repeat measure data capture allowed analysis for predictive outcomes.
- The cohort included prevalent and new cases Parkinson's disease. Although the varying disease duration of the Parkinson's disease cohort is a possible source of bias, we found no differences between the two groups survival.
- The control cohort included subjects without known neurological condition and thus may have intruded bias in the outcome comparisons with the Parkinson's disease patients.

Introduction

Data drawn from death certificates is often employed by epidemiological, public health and research scientists to capture the incidence, prevalence and mortality in populations. In addition, these statistics are often utilized in the evaluation of public health interventions, setting priorities for medical research and health services, the planning of health services, and the clinical assessment of the effectiveness of those services. [1-3] The introduction of the revised International Classification of Diseases (ICD) system in 2001 aim was to improve the accuracy in the reported cause of death, where underlying conditions, mentioned in Part 1 or 2 of death certification take priority over others. [4,5] The underlying principle for this is that reporting of multiple causes of death should provide a better description of a particular disease or condition, allowing for more effective and meaningful data capture. The reliability of statistical information extracted from death certificates however still remains uncertain, where for example, rather than the underlying chronic condition being reported, a secondary cause of death is often reported as the main cause of death. [6-14]

Increasing elderly population demographic changes worldwide along with exponential rises in chronic conditions, will most likely place greater social and fiscal demands on existing clinical heath and social services. [15] To ensure that mortality and survival rates are more precisely captured for these chronic conditions, the relative contributions different diseases have upon survival and mortality need to be more accurately measured. The challenge is to ensure that more reliable data are recorded to allow for more efficient planning for healthcare services and clinical interventions. Parkinson's disease (PD) is a progressive neurodegenerative disease strongly associated with increased mortality and lower life expectancy than the general population. [16] In addition to the motor symptoms of PD, many patients often live with a significant number of other non-motor conditions which contribute to the symptomatology of the disease. [17-22] In particular, dementia occurs frequently in the elderly PD patient and has been shown to be a strong predictor for increased mortality. [23-33] This most probably has implications for the quality of death certification, which in previous investigations has been found to be inconsistent, under recorded or an inaccurate record of the cause of death in patients. [16,34-37] The methodological design of previous investigations, where cohorts have been drawn from clinical populations or pharmaceutical trails alone may partially explain the variability between studies.[39-40] Only a small number of investigations have employed prospective community study methods to ascertain the utility of death certification in PD, and furthermore few have included a comparison control group.

This investigation is a report of the outcomes from a community cohort of PD patient and controls (without neurological disease) who have been regularly followed over the past 18 years in the county of Denbighshire in the United Kingdom. It aims firstly to examine the reported cause and quality of death certification in

these cohorts. Secondly, it will explore if PD and or dementia are reported as a cause or underling cause of death on certificates. Thirdly, the demographic, motor and non-motor symptoms of PD will be explored to establish if they are associated or predictive with an increased risk of mortality.

Methods

Subjects

The patient and control recruitment methodology has been described in greater depth in previous reports [25,41]. In brief, between December 1994 and January 1997, employing multiple sources of ascertainment we recruited newly diagnosed PD patients and patients with an existing diagnosis of probable PD based upon the UKPDS brain bank criteria. [42] General practitioner (GP) records (n=74) in a defined Area of North Wales (Denbighshire), were employed to identify individuals in receipt of a defined group of anti-parkinsonian drugs, which included Levodopa, monomine-oxidase-B inhibitors, dopamine agonists and anti-muscarinic drugs. Additionally, hospital records were examined and patients who were not on active but known to medical services were also ascertained. In total, 402 patients were identified, of whom 213 fulfilled criteria for clinically probable PD patients (n= 213). Of the original PD cohort, 25 died before they could be consented into the investigation, 13 withdrew consent and the remaining patients (n = 9) were lost to follow-up. This left at study entry 166 probable PD patients for follow-up from December 1997 to January 2015.

The control cohort was randomly drawn from two GP practices within the same geographical area of the PD cohort within the same time frame. The controls were matched for sex and age to PD patients ($\pm$ 3 years), were not known to have a diagnosis of clinically probable PD, parkinsonism, Alzheimer's or other dementia, stroke, neurological disorder, not in receipt of psychoactive drugs and did not have a known psychiatric, alcohol or substance abuse history. A total of 164 controls were invited to participate in the study, of whom 42 subsequently declined to participate and a further six withdrew consent at a later date. Upon initial baseline screening, eight were found to have previously suffered from a stroke, two had signs of parkinsonism and four fulfilled criteria for dementia and were excluded from further analysis, leaving a cohort of 102 control subjects.

Clinical assessment.

The PD cohort demographic variables were recorded which included age, gender, educational attainment, social class, age of PD diagnosis, and the duration of PD symptoms at study entry. They were also assessed with the Hoehn and Yahr staging (H&Y), the UPDRS motor subsection, the 15-item Geriatric Depression Scale (GDS -15), the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG), the Parkinson's disease Activities of Daily Living Scale (PADL) and the health

related quality of life (HRQoL) measure the EQ5-D.[43-47] These measures were reassessed at approximately two yearly intervals from the midpoint of the recruitment phase of the cohort assembly. Diagnosis of PD based upon UKPDBB criteria was reassessed (RJM) at review to ensure diagnostic accuracy was maintained. The control cohort screening was also carried out approximately every two years from study entry which included review and updating of demographic variables, and reassessment with the GDS-15, CAMCOG, and EQ5-D. Analysis of the clinical assessments was the most recent prior to a subjects reported death. The diagnosis of dementia for PD and controls 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. [48]

Death certification collection and evaluation.

Review of hospital and primary care records were employed to ascertain the number of individuals who were deceased. All of the death certificates in this investigation were obtained from the local Births, Deaths, and Marriages central record office for the PD and control cohorts. Primary and underlying cause of death, along with the age of the subject and the age of death are recorded on all certificates in the UK. In addition, all certificates completed by a doctor within the UK and are coded using the ICD-10 system as follows:
Ia: Disease or condition leading directly to death.
I(b): Other disease or condition, if any, leading to I(a).
I(c): Other disease or condition, if any, leading to I(b)
II: Other significant conditions that contributing to death but not related to the disease or condition causing it.

From the information recorded on the death certificates, we grouped primary and underlying causes of death in to nine further categories which were, PD, Sepsis, Dementia, Cerebrovascular, Cardiac, Cancer, Pneumonia, Chronic lung disease, other disorders.

Ethical approval:
This study was approved by the North Wales Research and ethics committee (Central).

Statistics.

The standardized mortality (SMR) was calculated as the ratio of observed deaths in the study group to expected deaths by employing age and gender specific morality rates for each year of the investigation, drawn from the UK Office of National Statistics interim life tables.

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 logrank statistics were employed to

examine between-group differences and between observed and expected survival curves (all values two-tailed, p<0.05). The survival time of subjects was calculated from the date of baseline examination. The Kaplan-Meier estimates were used to calculate the observed survival curves. Cox proportional hazard analysis was employed to investigate baseline demographic and clinical covariates were related to mortality. Covariates included in the models, age at study entry, Age at death, gender, motor function (PD cohort), mood, HRQol, and cognitive function. All data were analysed with the SPSS statistical package version 19. [49] The relative risk (RR) and 95% confidence interval (CI) were calculated using the Altman formula and MedCalc software. [50,51]

Results

From baseline to the study end date (30/01/2015), 158/166 (96%) of the PD and 34/102 (33%) of the control cohorts were decedents. In Table 1 the demographic and clinical outcomes of the PD and control cohorts are shown. Figure 1 illustrates the Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts. The SMR for the whole PD cohort was 1.82 (95% CI: 1.55 – 2.13). A sub group analysis between new cases of PD (n = 80) identified during the cases ascertainment phase of the investigation and existing cases of PD (n =78) revealed no excess mortality between the groups (p = 0.186) despite the varying disease duration. By 18 years the cumulative survival in the PD cohort (figure 1), was approximately 5% and 67% in the control cohort. The mortality risk controlled for age and gender was significantly higher risk in the PD cohort (HR 7.89, p = 0.0001). Older age at entry into the current stdy was predictive of an increased risk of mortality in both cohorts (PD: HR 1.06, p = 0.0001: Control: HR 1.09, p = 0.009). There were no statistical differences found between the PD and control cohorts age at death (PD cohort 80.7 (7.1), Control cohort 81.9(6.3); p = 0.552). The strongest predictor associated with mortality in the PD cohort after controlling for age and gender was worsening motor symptoms (HR 1.06, p< 0.01).

As a primary cause of death (Part 1a on UK death certificates), PD was recorded in just over 4% of the cohort. In sections 1b and 1c (conditions substantially contributing to death), PD was reported in 24% and 6% of cases respectively. In section II of the death certificates (co-morbid conditions substantially contributing to death); PD was reported in 19% of cases. Overall, PD as a contributing factor in the cause of death, was not reported anywhere on 75/158 (47%) of the PD cohort's certificates. The primary cause of death for the PD and control cohorts is shown in figures 2 & 3. The most common causes of death reported within the PD cohort (figure 2) were pneumonia (53%), followed by cardiac related deaths (21%). The most frequently recorded cause of death within the control cohort (figure 3) was cardiac disease (26%), cancer (24%), and pneumonia (18%). A comparison between the PD and Control cohorts revealed that the PD cohort were nearly three times more likely to have pneumonia recorded as a primary cause of death (RR, 2.94, 95% CI 1.40-6.19), Controlling

for patients and controls with dementia still revealed a higher risk of mortality in PD for pneumonia (RR, 2.03, 95% CI 1.34-3.6). The controls compared to the PD cohort had over a threefold increased risk of having a cancer related disorder recorded as a primary or underlying cause of death (RR, 3.72, 95% CI 1.58 -8.72).

Disease progression within the PD cohort was significantly associated with a worsening HRQoL at death ($p < 0.0001$). When compared to the controls, HRQoL was significantly poorer for the PD cohort ($p < 0.001$). At the time of death, 83/158 (52%) of the PD and 9/34 (26%) of the control cohorts were living in institutional care ($p < 0.003$). Overall, the PD cohort decedents had a threefold increased probability to be living in institutional care at death (RR 3.23, 95% CI 1.4-7.41). Controlling for age and duration of illness, the PD cohort living in institutional were also more likely to be demented (RR 2.7 (95% CI 1.21- 5.76). In contrast to the PD cohort, the control decedent's place of death was more likely to be in hospital (RR, 1.97, 1.48-2.62).

As a primary or underlying cause of death, dementia was underreported on both the PD and control certificates. Although 144/158 (91%) of the PD cohort had a diagnosis of dementia before their deaths, it was reported in only 14/144 of certificates. Similarly, only two of the control cohort had dementia recorded anywhere as a primary or underlying cause of death. Upon review however, a further four at the time of death had a confirmed diagnosis of dementia.

Discussion.

This investigation reports the cause of death recorded on the death certificates of PD and age matched control cohorts in Denbighshire in the UK. We have previously reported that the life expectancy and average age at death in this PD cohort is much lower than the general population. [16] In the current study the overall SMR for our PD cohort was 1.82, indicating an excess mortality. This is similar to previous investigations where the SMR has been reported to range from 0.9 to 3.8 [16] However, recent community based incident cohort and incident clinical cohort investigations have reported lower SMR's of 1.29 (95% CI, 0.97-1.61), and 1.39 (95% CI, 1.10.-1.50), suggesting a moderate increase mortality compared to the general population. [16,52] The shorter duration of PD diagnosis, lower number of recorded deaths and shorter follow-up period compared with the current investigation may partially explain these differences the current and previously reported UK investigation. In addition the other European investigation was limited by the retrospective analysis of a data set from 1978-1998 and recruitment solely from a clinical population.

Overall death certification and clinical research data appear to provide quite disparate mortality data in PD. Although our PD cohort had confirmed UKPDSBB criteria for probable PD, as a primary cause of death (Part 1a), it was recorded in just in over 4% of the cohort. A further 30% had PD recorded in parts 1b and c of their death certificates, and on Part II of certificates it was recorded

in a further 19% of cases. Overall, PD was not cited anywhere on 47% of the death certificates, which falls approximately midway with previous certification studies of between 14–70%. [16,34-37] The disparity reported between studies is most likely evidence of the differing methodologies employed such as, populations drawn from pharmaceutical trials alone, clinical samples, or retrospective case or chart record analysis.

Pneumonia was the most cited primary cause of death (52%), in the current study. This observation has also been frequently reported in other investigations. [16,52] Patients with PD, particularly as they become frailer with the progression of their illness, are at greater risk for pulmonary complications, due to obstructive ventilation dysfunction, upper airway dysfunction, and weakened strength of respiratory muscles. [53-55] The most frequently reported other causes of death were cardiovascular disease (21%), cerebrovascular disease (8%) and malignancy (6%).

This is the first study to our knowledge to describe underreporting of dementia as a primary, or underlying cause of death in a community based PD cohort. We have previously reported in this cohort the high prevalence of dementia of around 90%. [56] Upon review of the decedents death certificates, we found that less than 10% had any mention of dementia as an immediate or underlying cause of death. Previous general population investigations have also shown that rates of certification mentioning dementia as a main or underlying cause of death have been consistently under reported. [57-60] This perhaps is because certification tends to focus upon the immediate cause of death and does not really capture the multiple factors that contribute to death, particularly with elderly individuals with multiple co-morbidity.

This investigation found that the PD cohort were more likely than the controls to be living in a long term care setting before death. This may be a reflection of the duration, nature and the type of burden PD places upon relatives, especially those who have physical frailty themselves. Caring within the home setting may therefore become more impracticable and thus possibly precipitates entry into institutional care. The proportion of deaths in long term care amongst the PD cohort was also significantly higher than the control cohort. A recent study reported wide variations in the place of death of people with PD throughout the world, concluding that individual preference, social and socioeconomic circumstances; cultural, organisation and provision of health and palliative care all contribute to some extent the place of death. [61]

In common with previous mortality investigations we found fewer recorded cancer deaths within the PD cohort. [62] It is thought that mutations of the PARK2 (Parkin) gene found in 6-8% of PD patients may act in some cancers as a tumour suppressor proteins. [63] The absence or mutation of the Parkin gene is found in several tumour types, suggesting that the mechanisms of cell death in PD may play a role in the inhibition or formation of some cancers. [64,65] The decreased risk of mortality from cancer has also been

reported in other neurodegenerative disease including Alzheimer's, Huntington's disease and in populations where mild to moderate with cognitive impairment has also been observed. [66-69] Further studies are needed to explore the associations, risks, possible genetic markers and underling mechanisms in PD and other neurodegenerative conditions, to improve and identify and understand the role of cell death and its decreased cancer risk.

We would caution the message often given to PD patients that they die with, rather than die of the condition. The non-motor features of PD such as dementia and autonomic dysfunction are frequently observed in all stages of the disease and most likely make a significant contribution to mortality.[70] One recent investigation reported that autonomic dysfunction and dementia in PD was predictive of increased mortality particularly in patients with orthostatic hypotension (OH).[71] Another meta-analysis which explored the association with OH and mortality in general populations also concluded that OH may confer a greater risk (RR, 1.40) for mortality. [72] The association between the non-motor features of PD disease and mortality needs further research to understand and determine if these are causal or not.

This study's strengths are the robust follow-up over an 18-year period of a community based cohort all of whom fulfilled criteria for PD and diagnostic re-evaluation was reviewed regularly over this period to ensure diagnostic accuracy. The repeat measure design of the study also allowed us to control for demographics, and motor and non-motor symptomatology. The limitations of the study are that the PD cohort had a mix of prevalent and incident cases, thus possibly over estimating the possible causal associations with mortality. However, controlling for prevalent and incident cases in our analysis did not reveal any between group significant differences. In light of our findings we feel that the current methods of capturing the cause of death significantly underestimate the true population burden of PD. The under reporting of dementia as an underling cause of death in this cohort in addition to PD, also suggests that the interpretation of and quality of mortality data currently is not a valid or reliable source of data. Furthermore we would admonish the use of mortality statistics alone to plan for future service provision in this patient population.

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Figure legends:

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts.

Figure 2: Primary cause of death (Part 1a death certificates) reported for the PD cohort.

Figure 3: Primary cause of death (Part 1a death certificates) reported for the control cohort.

Table 1:
Demographic and clinical outcomes (Means, *standard deviations)* of the PD and control cohorts

	Parkinson's disease	Control	*p< 0.05*
Gender (female %)	44%	41%	NS
Age (entry into study)	74.2 (8.6)	74.8 (6.6)	NS
Age at death	80.7 (*7.1*)	81.9 (*6.3*)	NS
Institutional care %	52%	30%	0.003
Place of death (Hospital)	37%	74%	0.002
EQ-5D (Weighted health)	0.58 (*0.36*)	0.79 (*0.28*)	0.001
EQ-5D (VAS %)[1]	55 (*16.5*)	77 (*17.6*)	0.001
Onset of PD	67.3 (*10.7*)	------	-----
Duration of PD	13.2 (*8.8*)	------	-----
UPDRS (motor section)	27.9 (*11.7*)	------	-----
H & Y	2.9 (*0.74*)	------	-----
PADL	3.1 (*1.1*)	------	-----

[1] VAS = EQ-%D Visual analogue scale

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Competing interests: None declared.

Patient consent: All participants gave their informed and written consent on participation.

Data sharing statement: No additional data available.

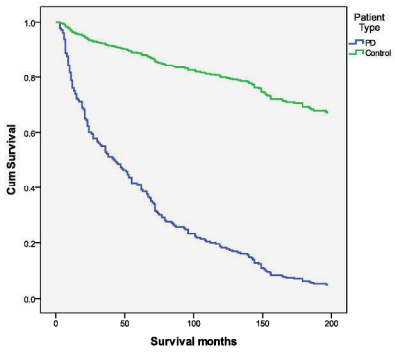

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts.

296x419mm (300 x 300 DPI)

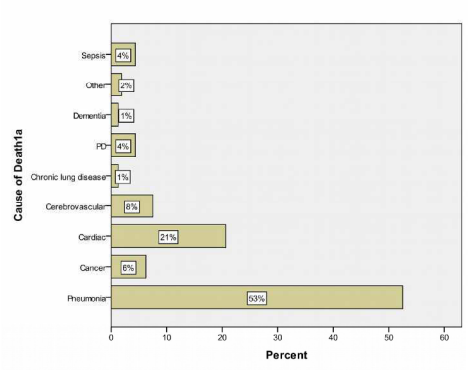

Figure 2: Primary cause of death (Part 1a death certificates) reported for the PD cohort.

297x420mm (300 x 300 DPI)

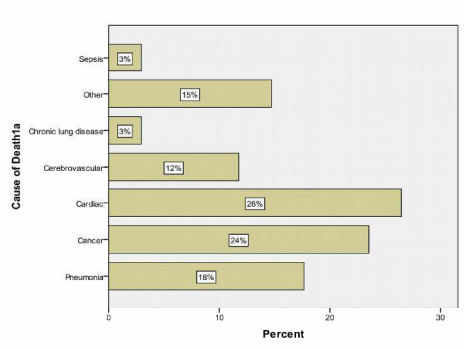

Figure 3: Primary cause of death (Part 1a death certificates) reported for the control cohort.

297x420mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,6,8
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5.6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	5,6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	5,6
		Cross-sectional study—Report numbers of outcome events or summary measures	--
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,6
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Mortality and the quality of death certification in cohort of Parkinson's disease and matched controls in North Wales United Kingdom at 18-years: a community based cohort study.

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Keywords:	Parkinson-s disease < NEUROLOGY, Mortality, Death certification, Dementia < NEUROLOGY

Mortality and the quality of death certification in cohort of Parkinson's disease and matched controls in North Wales United Kingdom at 18-years: a community based cohort study.

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Parkinson's disease, Mortality, Death certification, Dementia

Word count: 4030

Abstract

Objective: To estimate the survival, mortality and quality of death certification in a community cohort of Parkinson's disease (PD) patients and controls in North Wales United Kingdom (UK).
Setting and participants: A total of 166 PD patients and 102 controls were included in this investigation. Hospital and primary care records were employed to ascertain the number of individuals who died during the investigation period. The primary and underlying cause of death was extracted from certificates obtained from the UK General Register Office.
Results: There were 158 (95%) deaths in the PD and 34 (33%) deaths recorded in the control cohort. The Standard Mortality Rate (SMR) was 1.82 (95% CI: 1.55 – 2.13). The main cause of death reported in the PD cohort was pneumonia (53%), followed by cardiac related deaths (21%). PD as the primary or underlying cause was not reported in 75/158 (47%) of the cohort. In addition, although 144 of the cohort had a diagnosis of dementia, this was reported in less than 10% (n=14) of their death certificates.
Conclusion: This community based investigation established that PD is associated with a higher risk of mortality compared to the general population. In addition, we found that the majority of patients with PD if they survive long enough will develop dementia. However, the reporting of PD and dementia as a cause or underlying cause of death on certificates was found to be suboptimal. The results from this investigation suggest that use of mortality statistics derived from death certification alone in epidemiological studies, healthcare planning and provision need to be reconsidered, because they are not a valid or reliable source of data capture.

Strengths and limitations

- Community based longitudinal follow-up cohort design.
- All patients fulfilled diagnostic criteria for Parkinson's disease and or dementia.
- Baseline and subsequent repeat measure data capture allowed analysis for predictive outcomes.
- The cohort included prevalent and new cases Parkinson's disease. Although the varying disease duration of the Parkinson's disease cohort is a possible source of bias, we found no differences between the two groups survival.
- The control cohort included subjects without known neurological condition and thus may have intruded bias in the outcome comparisons with the Parkinson's disease patients.

Introduction

Data drawn from death certificates is often employed by epidemiological, public health and research scientists to capture the incidence, prevalence and mortality in populations. In addition, these statistics are often utilized in the evaluation of public health interventions, setting priorities for medical research and health services, the planning of health services, and the clinical assessment of the effectiveness of those services. [1-3] The introduction of the revised International Classification of Diseases (ICD) system in 2001 aim was to improve the accuracy in the reported cause of death, where underlying conditions, mentioned in Part 1 or 2 of death certification take priority over others. [4,5] The underlying principle for this is that reporting of multiple causes of death should provide a better description of a particular disease or condition, allowing for more effective and meaningful data capture. The reliability of statistical information extracted from death certificates however still remains uncertain, where for example, rather than the underlying chronic condition being reported, a secondary cause of death is often reported as the main cause of death. [6-14]

Increasing demographic changes worldwide in elderly populations along with exponential rises in chronic conditions will most likely place greater social and fiscal demands on existing clinical, health and social services. [15] To ensure that mortality and survival rates are more precisely captured for these chronic conditions, the relative contributions different diseases have upon survival and mortality need to be more accurately measured. The challenge is to ensure that more reliable data are recorded to allow for more efficient planning for healthcare services and clinical interventions. Parkinson's disease (PD) is a progressive neurodegenerative disease strongly associated with increased mortality and lower life expectancy than the general population. [16] In addition to the motor symptoms of PD, many patients often live with a significant number of other non-motor conditions which contribute to the symptomatology of the disease. [17-22] In particular, dementia occurs frequently in the elderly PD patient and has been shown to be a strong predictor for increased mortality. [23-33] This most probably has implications for the quality of death certification, which in previous investigations has been found to be inconsistent, under recorded or an inaccurate record of the cause of death in patients. [16,34-37] The methodological design of previous investigations, where cohorts have been drawn from clinical populations or pharmaceutical trials alone may partially explain the variability between studies.[38-40] Only a small number of investigations have employed prospective community study methods to ascertain the utility of death certification in PD, and furthermore few have included a comparison control group.

This investigation is a report of the outcomes from a community cohort of PD patient and controls (without neurological disease) who have been regularly followed over the past 18 years in the county of Denbighshire in the United Kingdom. It aims firstly to examine the reported cause and quality of death certification in

these cohorts. Secondly, it will explore if PD and or dementia are reported as a cause or underling cause of death on certificates. Thirdly, the demographic, motor and non-motor symptoms of PD will be explored to establish if they are associated or predictive with an increased risk of mortality.

Methods

Subjects

The patient and control recruitment methodology has been described in greater depth in previous reports [25,41]. In brief, between December 1994 and January 1997, employing multiple sources of ascertainment we recruited newly diagnosed PD patients and patients with an existing diagnosis of probable PD based upon the UKPDS brain bank criteria. [42] General practitioner (GP) records (n=74) in a defined Area of North Wales (Denbighshire), were employed to identify individuals in receipt of a defined group of anti-parkinsonian drugs, which included Levodopa, monomine-oxidase-B inhibitors, dopamine agonists and anti-muscarinic drugs. Additionally, hospital records were examined and patients who were not on active but known to medical services were also ascertained. In total, 402 patients were identified, of whom 213 fulfilled criteria for clinically probable PD patients (n= 213). Of the original PD cohort, 25 died before they could be consented into the investigation, 13 withdrew consent and the remaining patients (n = 9) were lost to follow-up. This left at study entry 166 probable PD patients for follow-up from December 1997 to January 2015.

The control cohort was randomly drawn from two GP practices within the same geographical area of the PD cohort within the same time frame. The controls were matched for sex and age to PD patients ($\pm$ 3 years), were not known to have a diagnosis of clinically probable PD, parkinsonism, Alzheimer's or other dementia, stroke, neurological disorder, not in receipt of psychoactive drugs and did not have a known psychiatric, alcohol or substance abuse history. A total of 164 controls were invited to participate in the study, of whom 42 subsequently declined to participate and a further six withdrew consent at a later date. Upon initial baseline screening, eight were found to have previously suffered from a stroke, two had signs of parkinsonism and four fulfilled criteria for dementia and were excluded from further analysis, leaving a cohort of 102 control subjects.

Clinical assessment.

The PD and control cohorts demographic details were recorded which included, age, gender, educational attainment, social class, and smoking history. In addition to the demographic details, PD specific variables were also recorded which included, age of diagnosis, duration of symptoms, Hoehn and Yahr staging (H&Y), the UPDRS motor subsection, the 15-item Geriatric Depression Scale (GDS -15), the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG), the Parkinson's

disease Activities of Daily Living Scale (PADL) and the health related quality of life (HRQoL) measure the EQ5-D.[43-47] These measures were reassessed at approximately two yearly intervals from the midpoint of the recruitment phase of the cohort assembly. Diagnosis of PD based upon UKPDBB criteria was reassessed (RJM) at review to ensure diagnostic accuracy was maintained. The control cohort screening was also carried out approximately every two years from study entry which included review and updating of demographic variables, and reassessment with the GDS-15, CAMCOG, and EQ5-D. Analysis of the clinical assessments was the most recent prior to a subjects reported death. The diagnosis of dementia for PD and controls 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. [48]

Death certification collection and evaluation.

Review of hospital and primary care records were employed to ascertain the number of individuals who were deceased. All of the death certificates in this investigation were obtained from the local Births, Deaths, and Marriages central record office for the PD and control cohorts. Primary and underlying cause of death, along with the age of the subject and the age of death are recorded on all certificates in the UK. In addition, all certificates completed by a doctor within the UK and are coded using the ICD-10 system as follows:
Ia: Disease or condition leading directly to death.
I(b): Other disease or condition, if any, leading to I(a).
I(c): Other disease or condition, if any, leading to I(b)
II: Other significant conditions that contributing to death but not related to the disease or condition causing it.

From the information recorded on the death certificates, we grouped primary and underlying causes of death in to nine further categories which were, PD, Sepsis, Dementia, Cerebrovascular, Cardiac, Cancer, Pneumonia, Chronic lung disease, other disorders.

Ethical approval:
This study was approved by the North Wales Research and ethics committee (Central).

Statistics.

The standardized mortality (SMR) was calculated as the ratio of observed deaths in the study group to expected deaths by employing age and gender specific morality rates for each year of the investigation, drawn from the UK Office of National Statistics interim life tables.

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 logrank statistics were employed to examine between-group differences and between observed and expected survival curves (all values two-tailed, $p<0.05$). The survival time of subjects was calculated from the date of baseline examination. The Kaplan-Meier estimates were used to calculate the observed survival curves. Cox proportional (PH) hazards analysis was employed to investigate the effect of several variables upon the time a specified event takes to happen, which in the current study was death. To satisfy the assumptions for the PH modelling, visual inspections of the residuals against the independent variable were made. This was carried out by plotting the cumulative survival function for each group against time and observing if the lines were parallel, proportional hazard was assumed. In addition, the -2 log likelihood ratio statistic was employed to determine how well the model (pattern of covariates) fitted the obtained data. The PH model covariates act as factors multiplying the hazard rate, which is the probability of experiencing the event which in this study is death. Covariates included in the PH model included, age at study entry, age at death, gender, motor function, mood, HRQol, and cognitive function. The Hazard Ratio (HR) reported in this study provides an estimate of the relative risk.

All data were analysed with the SPSS statistical package version 19. [49] The relative risk (RR) and 95% confidence interval (CI) were calculated using the Altman formula and MedCalc software. [50,51]

Results

From baseline to the study end date (30/01/2015), 158/166 (96%) of the PD and 34/102 (33%) of the control cohorts were decedents. In Table 1 the demographic and clinical outcomes of the PD and control cohorts are shown. Figure 1 illustrates the Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts. The SMR for the whole PD cohort was 1.82 (95% CI: 1.55 – 2.13). A sub group analysis between new cases of PD (n = 80) identified during the cases ascertainment phase of the investigation and existing cases of PD (n =78) revealed no excess mortality between the groups ($p = 0.186$) despite the varying disease duration. By 18 years the cumulative survival in the PD cohort (figure 1), was approximately 5% and 67% in the control cohort. The mortality risk controlled for age and gender was significantly higher risk in the PD cohort (HR 7.89, $p = 0.0001$). Older age at entry into the current study was predictive of an increased risk of mortality in both cohorts (PD: HR 1.06, $p = 0.0001$: Control: HR 1.09, $p = 0.009$). There were no statistical differences found between the PD and control cohorts age at death (PD cohort 80.7 (7.1), Control cohort 81.9(6.3); $p = 0.552$). The strongest predictor associated with mortality in the PD cohort after controlling for age and gender was worsening motor symptoms (HR 1.06, $p< 0.01$).

As a primary cause of death (Part 1a on UK death certificates), PD was recorded in just over 4% of the cohort. In sections 1b and 1c (conditions substantially contributing to death), PD was reported in 24% and 6% of cases respectively. In section II of the death

certificates (co-morbid conditions substantially contributing to death); PD was reported in 19% of cases. Overall, PD as a contributing factor in the cause of death, was not reported anywhere on 75/158 (47%) of the PD cohort's certificates. The primary cause of death for the PD and control cohorts is shown in Table 2. The most common causes of death reported within the PD cohort were pneumonia (53%), followed by cardiac related deaths (21%). The most frequently recorded cause of death within the control cohort were cardiac disease (26%), cancer (24%), and pneumonia (18%). A comparison between the PD and Control cohorts revealed that the PD cohort were nearly three times more likely to have pneumonia recorded as a primary cause of death (RR, 2.94, 95% CI 1.40-6.19), Controlling for patients and controls with dementia still revealed a higher risk of mortality in PD for pneumonia (RR, 2.03, 95% CI 1.34-3.6). The controls compared to the PD cohort had over a threefold increased risk of having a cancer related disorder recorded as a primary or underlying cause of death (RR, 3.72, 95% CI 1.58 -8.72). Examining the smoking history between the two cohorts found no significant differences with the frequency of current or former smokers ($p = 0.39$), nor were there differences in the cancer risk observed between the PD and controls cohorts who never smoked ($p = 0.75$). However, significantly more of the controls who were smokers prior to their death had cancer recorded as a primary or secondary cause of death ($p < 0.025$).

Disease progression within the PD cohort was significantly associated with a worsening HRQoL at death ($p < 0.0001$). When compared to the controls, HRQoL was significantly poorer for the PD cohort ($p < 0.001$). At the time of death, 83/158 (52%) of the PD and 9/34 (26%) of the control cohorts were living in institutional care ($p < 0.003$). Overall, the PD cohort decedents had a threefold increased probability to be living in institutional care at death (RR 3.23, 95% CI 1.4-7.41). Controlling for age and duration of illness, the PD cohort living in institutional were also more likely to be demented (RR 2.7 (95% CI 1.21- 5.76). In contrast to the PD cohort, the control decedent's place of death was more likely to be in hospital (RR, 1.97, 1.48-2.62).

As a primary or underlying cause of death, dementia was underreported on both the PD and control certificates. Although 144/158 (91%) of the PD cohort had a diagnosis of dementia before their deaths, it was reported in only 14/144 of certificates. Similarly, only two of the control cohort had dementia recorded anywhere as a primary or underlying cause of death. Upon review however, a further four at the time of death had a confirmed diagnosis of dementia.

Discussion.

This investigation reports the cause of death recorded on the death certificates of PD and age matched control cohorts in Denbighshire

in the UK. We have previously reported that the life expectancy and average age at death in this PD cohort is much lower than the general population. [16] In the current study the overall SMR for our PD cohort was 1.82, indicating an excess mortality. This is similar to previous investigations where the SMR has been reported to range from 0.9 to 3.8 [16] However, recent community based incident cohort and incident clinical cohort investigations have reported lower SMR's of 1.29 (95% CI, 0.97-1.61), and 1.39 (95% CI, 1.10.-1.50), suggesting a moderate increase mortality compared to the general population. [16,52] The shorter duration of PD diagnosis, lower number of recorded deaths and shorter follow-up period compared with the current investigation may partially explain these differences the current and previously reported UK investigation. In addition the other European investigation was limited by the retrospective analysis of a data set from 1978-1998 and recruitment solely from a clinical population.

Overall death certification and clinical research data appear to provide quite disparate mortality data in PD. Although our PD cohort had confirmed UKPDSBB criteria for probable PD, as a primary cause of death (Part 1a), it was recorded in just in over 4% of the cohort. A further 30% had PD recorded in parts 1b and c of their death certificates, and on Part II of certificates it was recorded in a further 19% of cases. Overall, PD was not cited anywhere on 47% of the death certificates, which falls approximately midway with previous certification studies of between 14–70%. [16,34-37] The disparity reported between studies is most likely evidence of the differing methodologies employed such as, populations drawn from pharmaceutical trials alone, clinical samples, or retrospective case or chart record analysis.

Pneumonia was the most cited primary cause of death (52%), in the current study. This observation has also been frequently reported in other investigations. [16,52] Patients with PD, particularly as they become frailer with the progression of their illness, are at greater risk for pulmonary complications, due to obstructive ventilation dysfunction, upper airway dysfunction, and weakened strength of respiratory muscles. [53-55] The most frequently reported other causes of death were cardiovascular disease (21%), cerebrovascular disease (8%) and malignancy (6%).

This is the first study to our knowledge to describe underreporting of dementia as a primary, or underlying cause of death in a community based PD cohort. We have previously reported in this cohort the high prevalence of dementia of around 90%. [56] Upon review of the decedents death certificates, we found that less than 10% had any mention of dementia as an immediate or underlying cause of death. Previous general population investigations have also shown that rates of certification mentioning dementia as a main or underlying cause of death have been consistently under reported. [57-61] This perhaps is because certification tends to focus upon the immediate cause of death and does not really capture the multiple factors that contribute to death, particularly with elderly individuals with multiple co-morbidity.

This investigation found that the PD cohort were more likely than the controls to be living in a long term care setting before death. This may be a reflection of the duration, nature and the type of burden PD places upon relatives, especially those who have physical frailty themselves. Caring within the home setting may therefore become more impracticable and thus possibly precipitates entry into institutional care. The proportion of deaths in long term care amongst the PD cohort was also significantly higher than the control cohort. A recent study reported wide variations in the place of death of people with PD throughout the world, concluding that individual preference, social and socioeconomic circumstances; cultural, organisation and provision of health and palliative care all contribute to some extent the place of death. [62]

In common with previous mortality investigations we found fewer recorded cancer deaths within the PD cohort. [63] We did not observe differences in the current or past smoking history frequency between our cohorts. Similarly no differences were revealed between the cohorts and cancer risk in those who had never smoked. There were no differences seen in the types of cancer type on death certificates compared to smokers and non-smokers. However, in the current smoker groups prior to death, significantly more cancer associated deaths were recorded in the controls compared to the PD cohort. A possible explanation for this disparity may be that mutations of the PARK2 (Parkin) gene found in 6-8% of PD patients, may act in some cancers as a tumour suppressor proteins. [64] The absence or mutation of the Parkin gene is found in several tumour types, suggesting that the mechanisms of cell death in PD may play a role in the inhibition or formation of some cancers. [64,65] The decreased risk of mortality from cancer has also been reported in other neurodegenerative disease including Alzheimer's, Huntington's disease and in populations where mild to moderate with cognitive impairment has also been observed. [66-69] Further studies are needed to explore the associations, risks, possible genetic markers and underling mechanisms in PD and other neurodegenerative conditions, to improve and identify and understand the role of cell death and its decreased cancer risk.

We would caution the message often given to PD patients that they die with, rather than die of the condition. The non-motor features of PD such as dementia and autonomic dysfunction are frequently observed in all stages of the disease and most likely make a significant contribution to mortality.[70] One recent investigation reported that autonomic dysfunction and dementia in PD was predictive of increased mortality particularly in patients with orthostatic hypotension (OH).[71] Another meta-analysis which explored the association with OH and mortality in general populations also concluded that OH may confer a greater risk (RR, 1.40) for mortality. [72] The association between the non-motor features of PD disease and mortality needs further research to understand and determine if these are causal or not.

This study's strengths are the robust follow-up over an 18-year period of a community based cohort all of whom fulfilled criteria for PD and diagnostic re-evaluation was reviewed regularly over this period to ensure diagnostic accuracy. The repeat measure design of the study also allowed us to control for demographics, and motor and non-motor symptomatology. The limitations of the study are that the PD cohort had a mix of prevalent and incident cases, thus possibly over estimating the possible causal associations with mortality. However, controlling for prevalent and incident cases in our analysis did not reveal any between group significant differences. Our control cohort was selected carefully in terms of age, gender, and disease exposure and may not representative of the general population. We endeavoured to reduce this potential bias by randomly selecting controls from general practitioner lists within defined catchment area as the PD cohort. However, excluding controls with known neurological, psychiatric illness and possibly healthier general health may be a potential source of error. The ideal comparison group in a cohort study would be exactly the same as the cohort of interest, except that they would not have the condition under investigation. In older populations, the selection of any control group is often a compromise in ensuring that the control group differs enough with respect to the condition of interest, yet are similar as possible to explore what other factors influence the outcome under investigation. We believe that our selection of controls without neurological or psychiatric disease allowed us to control for confounding factors in the analysis in both cohorts that would not have been possible in the general population.

In light of our findings we feel that the current methods of capturing the cause of death by certification will significantly underestimate the true population burden of PD. The under reporting of dementia as an underling cause of death in this cohort in addition to PD, also suggests that the interpretation of and quality of mortality data currently is not a valid or reliable source of data. Furthermore we would admonish the use of mortality statistics alone to plan for future service provision in this patient population.

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Table 1:
Demographic and clinical outcomes (Means, *standard deviations)* of the PD and control cohorts

	Parkinson's disease	Control	*p< 0.05*
Gender (female %)	44%	41%	NS
Age (entry into study)	74.2 (8.6)	74.8 (6.6)	NS
Age at death	80.7 (*7.1*)	81.9 (*6.3*)	NS
Institutional care %	52%	30%	0.003
Place of death (Hospital)	37%	74%	0.002
EQ-5D (Weighted health)	0.58 (*0.36*)	0.79 (*0.28*)	0.001
EQ-5D (VAS %)[1]	55 (*16.5*)	77 (*17.6*)	0.001
Onset of PD	67.3 (*10.7*)	------	-----
Duration of PD	13.2 (*8.8*)	------	-----
UPDRS (motor section)	27.9 (*11.7*)	------	-----
H & Y	2.9 (*0.74*)	------	-----
PADL	3.1 (*1.1*)	------	-----

[1] VAS = EQ-5D Visual Analogue Scale.

Table 2.

Primary cause of death (Part 1a death certificates) reported for the PD (n =158) and control (n =34) cohorts.

	Parkinson's disease	Control
Pneumonia	84 (53.2%)	6 (17.6%)
Cardiac	33 (20.9%)	9 (26.5%)
Cancer	10 (6.3%)	8 (23.5%)
Cerebrovascular	12 (7.6%)	4 (11.8%)
Parkinson's disease	7 (4.4%)	0
Other*	12	7

* Other includes Sepsis; Dementia; Immobility; Chronic obstructive pulmonary disease; Old age; Fracture neck of Femur; Multi-organ failure; Motor Neurone disease.

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts

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Contributors: PH and RJM conceived and designed the study, collected the data, and managed the database. PH managed the database, contributed to data cleaning, performed the statistical analyses. PH and RJM contributed to interpretation of the data. PH and RJM wrote the manuscript. All authors critically reviewed the manuscript and approved the final version to be published.

Competing interests: None declared.

Patient consent: All participants gave their informed and written consent on participation.

Data sharing statement: No additional data available.

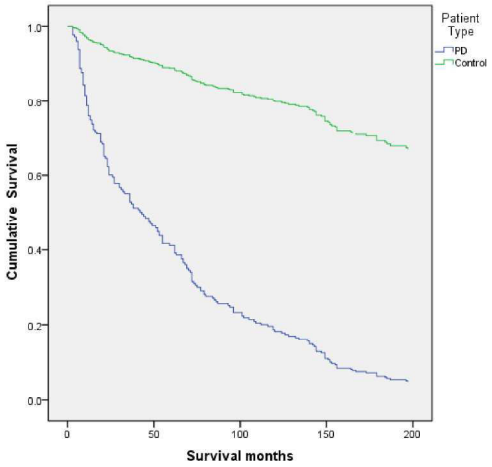

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts

297x420mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,6,8
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5.6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	5,6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	5,6
		Cross-sectional study—Report numbers of outcome events or summary measures	--
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,6
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Mortality and the quality of death certification in a cohort of Parkinson's disease patients and matched controls in North Wales, United Kingdom at 18-years: a community based cohort study.

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Mortality and the quality of death certification in a cohort of Parkinson's disease patients and matched controls in North Wales, United Kingdom at 18-years: a community based cohort study.

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Word count: 3685

Abstract

Objective: This investigation reports the cause and the quality of death certification in a community cohort of Parkinson's disease (PD) patients and controls at 18 years.
Setting: Denbighshire North Wales United Kingdom (UK).
Participants: The community based cohorts consisted of 166 PD and 102 matched controls.
Primary outcomes: All-cause mortality was ascertained at 18-years by review of hospital, primary care records and examination of death certificates obtained form the UK General Register Office. Mortality Hazard Ratios were estimated using Cox proportional regression controlling for covariates including, age at study entry, age at death, gender, motor function, mood, health related quality of life (HRQoL), and cognitive function.
Results: After 18-years, 158(95%) of the PD cohort and 34(33%) of the control cohort had died. Compared to the general UK population, the PD cohort had a higher risk of mortality (standard mortality rate, 1.82, 95% CI: 1.55 – 2.13). As the primary or underlying cause of death, PD was not reported in 75/158 (47%) of the death certificates. In addition, although 144/158 (91%) of the PD cohort had a diagnosis of dementia, this was reported in less than 10% of death certificates. The main cause of death reported in the PD cohort was pneumonia (53%), followed by cardiac related deaths (21%). Compared to controls, PD patients had a greater risk of pneumonia (2.03, 95% CI, 1.34-3.6), poorer HRQoL and more likely to reside in institutional care at death ($p < 0.01$).
Conclusion: This investigation found that PD was associated with an excess risk of mortality compared to the general population. However, PD as a primary or underlying cause of death recorded on certificates was found to be suboptimal. This suggests that the quality of mortality statistics drawn from death certificates alone is not a valid or reliable source of data.

Strengths and limitations

- Community based longitudinal follow-up cohort design.
- All patients fulfilled diagnostic criteria for Parkinson's disease and or dementia.
- Baseline and subsequent repeat measure data capture allowed analysis for predictive outcomes.
- The cohort included prevalent and new cases Parkinson's disease. Although the varying disease duration of the Parkinson's disease cohort is a possible source of bias, we found no differences between the two groups survival.
- The control cohort included subjects without known neurological conditions and thus may have intruded bias in the outcome comparisons with the Parkinson's disease patients.

Introduction

Data drawn from death certificates is often employed by epidemiological, public health and research scientists to capture the incidence, prevalence and mortality in populations. In addition, these statistics are often utilized in the evaluation of public health interventions, setting priorities for medical research and health services, the planning of health services, and the clinical assessment of the effectiveness of those services. [1-3] The introduction of the revised International Classification of Diseases (ICD) system in 2001 aim was to improve the accuracy in the reported cause of death, where underlying conditions, mentioned in Part 1 or 2 of death certification take priority over others. [4,5] The underlying principle for this is that reporting of multiple causes of death should provide a better description of a particular disease or condition, allowing for more effective and meaningful data capture. The reliability of statistical information extracted from death certificates remains uncertain, where for example, rather than the underlying chronic condition being reported, a secondary cause of death is often reported as the main cause of death. [6-14]

The projected elderly population demographic changes worldwide, along with exponential rises in chronic conditions will most likely place greater social and fiscal demands upon existing clinical, health and social services. [15] To ensure that mortality and survival rates are more precisely captured for these chronic conditions, the relative contributions different diseases have upon survival and mortality need to be more accurately measured. The challenge is to ensure that any statistical collected is valid and reliable enough to allow for more efficient planning for healthcare services and clinical interventions. Parkinson's disease (PD) is a progressive neurodegenerative disease strongly associated with increased mortality and lower life expectancy than the general population. [16] In addition to the motor symptoms of PD, many patients often live with a significant number of other non-motor conditions, which contribute, to the symptomatology of the disease. [17-22] In particular, dementia occurs frequently in the elderly PD patient and has been shown to be a strong predictor for increased mortality. [23-33] This most probably has implications for the quality of death certification, which in previous investigations has been found to be inconsistent, under recorded or an inaccurate record of the cause of death in patients. [16,34-38] The methodological design of previous investigations, where cohorts have been drawn from clinical populations or pharmaceutical trails alone may partially explain the variability between studies.[39-40] Only a small number of investigations have employed prospective community study methods to ascertain the utility of death certification in PD, and furthermore few have included a comparison control group.

This investigation is a report of the outcomes from a community cohort of PD patient and controls (without neurological disease) who have been regularly followed over the past 18 years in the county of Denbighshire in the United Kingdom. It aims firstly to examine the reported cause and quality of death certification in these cohorts. Secondly, it will explore if PD and or dementia are

reported as a cause or underling cause of death on certificates. Thirdly, the demographic, motor and non-motor symptoms of PD will be explored to establish if they are associated or predictive with an increased risk of mortality.

Methods

Subjects

The patient and control recruitment methodology has been described in greater depth in previous reports [25,41]. In brief, between December 1994 and January 1997, employing multiple sources of ascertainment we recruited newly diagnosed PD patients and patients with an existing diagnosis of probable PD based upon the UKPDS brain bank criteria. [42] General practitioner (GP) records (n=74) in a defined Area of North Wales (Denbighshire), were employed to identify individuals in receipt of a defined group of anti-parkinsonian drugs, which included Levodopa, monomine-oxidase-B inhibitors, dopamine agonists and anti-muscarinic drugs. Additionally, hospital records were examined and patients who were not on active but known to medical services were also ascertained. In total, 402 patients were identified, of whom 213 fulfilled criteria for clinically probable PD patients (n= 213). Of the original PD cohort, 25 died before they could be consented into the investigation, 13 withdrew consent and the remaining patients (n = 9) were lost to follow-up. This left at study entry 166 probable PD patients for follow-up from December 1997 to January 2015.

The control cohort was randomly drawn from two GP practices within the same geographical area of the PD cohort within the same time frame. The controls were matched for sex and age to PD patients (± 3 years), were not known to have a diagnosis of clinically probable PD, parkinsonism, Alzheimer's or other dementia, stroke, neurological disorder, not in receipt of psychoactive drugs and did not have a known psychiatric, alcohol or substance abuse history. One hundred and sixty four controls were invited to participate in the study, of whom 42 subsequently declined to participate and a further six withdrew consent at a later date. Upon initial baseline screening, eight were found to have previously suffered from a stroke, two had signs of parkinsonism and four fulfilled criteria for dementia and were excluded from further analysis, leaving a cohort of 102 control subjects.

Clinical assessment.

The PD and control cohorts demographic details were recorded which included, age, gender, educational attainment, social class, and smoking history. In addition to the demographic details, PD specific variables were also recorded which included, age of diagnosis, duration of symptoms, Hoehn and Yahr staging (H&Y), the UPDRS motor subsection, the 15-item Geriatric Depression Scale (GDS -15), the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), section B (CAMCOG), the Parkinson's disease Activities of Daily Living Scale (PADL) and the health

related quality of life (HRQoL) measure the EQ5-D. [43-47] These measures were reassessed at approximately two yearly intervals from the midpoint of the recruitment phase of the cohort assembly. Diagnosis of PD based upon UKPDBB criteria was reassessed (RJM) at review to ensure diagnostic accuracy was maintained. The control cohort screening was also carried out approximately every two years from study entry, which included review and updating of demographic variables, and reassessment with the GDS-15, CAMCOG, and EQ5-D. Analysis of the clinical assessments was the most recent prior to a subjects reported death. The diagnosis of dementia for PD and controls 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. [48]

Death certification collection and evaluation.

Review of hospital and primary care records were employed to ascertain the number of individuals who were deceased. All of the death certificates in this investigation were obtained from the local Births, Deaths, and Marriages central record office for the PD and control cohorts. Primary and underlying cause of death, along with the age of the subject and the age of death are recorded on all certificates in the UK. In addition, all certificates completed by a doctor within the UK and are coded using the ICD-10 system as follows:
Ia: Disease or condition leading directly to death.
I(b): Other disease or condition, if any, leading to I(a).
I(c): Other disease or condition, if any, leading to I(b)
II: Other significant conditions that contributing to death but not related to the disease or condition causing it.

From the information recorded on the death certificates, we grouped primary and underlying causes of death in to nine further categories which were, PD, Sepsis, Dementia, Cerebrovascular, Cardiac, Cancer, Pneumonia, Chronic lung disease, other disorders.

Ethical approval:
This study was approved by the North Wales Research and ethics committee (Central).

Statistics.

The age and gender specific standardized mortality ratios (SMR) were calculated by dividing the observed deaths in each cohort by expected numbers of deaths. This is calculated by multiplication of the numbers of person's-years for each 5-year age group, gender and year by the corresponding general population age group, gender and year, drawn from the UK Office of National Statistics interim life tables 2016.

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 logrank statistics were employed to examine between-group differences and between observed and expected survival curves. The Relative Risk (RR) was calculated by dividing the probability of an event occurring for PD cohort, divided by the probability of an event occurring for the control cohort. The survival time of subjects was calculated from the date of baseline examination for each subject. The Kaplan-Meier estimates were used to calculate the observed survival curves. Cox proportional hazards (PH) analysis was used to investigate the effect of several variables upon the time a specified event takes to happen. To satisfy the assumptions for the PH modelling, visual inspections of the Kaplan-Meier curves were made. The Cox PH modelling was also employed to calculate the hazard ratio's (HR) and the 95% confidence intervals (CIs) for differences between groups defined by demographic and clinical features defined at baseline The PH model covariates act as factors multiplying the (HR), which is the probability of experiencing the event, which in this study is death. Covariates included in the PH model included, age at study entry, age at death, gender, motor function, mood, HRQol, and cognitive function. The Hazard Ratio (HR) reported in this study provides an estimate of the relative risk.

All data were analysed with the SPSS statistical package version 19 and the RR and 95% CIs were calculated using the Altman formula and MedCalc software. [49-51] The level of significance was set at as $p<0.05$.

Results

From baseline to the study end date (30/01/2015), 158/166 (96%) of the PD and 34/102 (33%) of the control cohorts were decedents. In Table 1 the demographic and clinical outcomes of the PD and control cohorts are shown. Figure 1 illustrates the Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts. The SMR for the whole PD cohort was 1.82 (95% CI: 1.55 – 2.13). A sub group analysis between new cases of PD (n = 80) identified during the cases ascertainment phase of the investigation and existing cases of PD (n =78) revealed no excess mortality between the groups ($p = 0.186$) despite the varying disease duration. By 18 years the cumulative survival in the PD cohort (figure 1), was approximately 5% and 67% in the control cohort. The mortality risk controlled for age and gender was significantly higher risk in the PD cohort (HR 7.89, $p = 0.0001$). Older age at entry into the current study was predictive of an increased risk of mortality in both cohorts (PD: HR 1.06, $p = 0.0001$: Control: HR 1.09, $p = 0.009$). There were no statistical differences found between the PD and control cohorts age at death (PD cohort 80.7 (7.1), Control cohort 81.9(6.3); $p = 0.552$). The strongest predictor associated with mortality in the PD cohort after controlling for age and gender was worsening motor symptoms (HR 1.06, $p< 0.01$).

As a primary cause of death (Part 1a on UK death certificates), PD was recorded in just over 4% of the cohort. In sections 1b and 1c (conditions substantially contributing to death), PD was reported in

24% and 6% of cases respectively. In Section II of the death certificates (co-morbid conditions substantially contributing to death); PD was reported in 19% of cases. Overall, PD as a contributing factor in the cause of death, was not reported anywhere on 75/158 (47%) of the PD cohort's certificates. The primary cause of death for the PD and control cohorts is given in Table 2 . The most common causes of death reported within the PD cohort were pneumonia (53%), followed by cardiac related deaths (21%). The most frequently recorded cause of death within the control cohort was cardiac disease (26%), cancer (24%), and pneumonia (18%). A comparison between the PD and Control cohorts revealed that the PD cohort were nearly three times more likely to have pneumonia recorded as a primary cause of death (RR, 2.94, 95% CI 1.40-6.19), Controlling for patients and controls with dementia still revealed a higher risk of mortality in PD for pneumonia (RR, 2.03, 95% CI 1.34-3.6). The controls compared to the PD cohort had over a threefold increased risk of having a cancer related disorder recorded as a primary or underlying cause of death (RR, 3.72, 95% CI 1.58 -8.72). Examining the smoking history between the two cohorts found no significant differences with the frequency of current or former smokers ($p = 0.39$), nor were differences in cancer risk observed between the PD and controls cohorts who never smoked ($p = 0.75$). However, significantly more of the controls who were smokers prior to their death had cancer recorded as a primary or secondary cause of death ($p < 0.025$).

Disease progression within the PD cohort was significantly associated with a worsening HRQoL at death ($p < 0.0001$). When compared to the controls, HRQoL was significantly poorer for the PD cohort ($p < 0.001$). At the time of death, 83/158 (52%) of the PD and 9/34 (26%) of the control cohorts were living in institutional care ($p < 0.003$). Overall, the PD cohort decedents had a threefold increased probability to be living in institutional care at death (RR 3.23, 95% CI 1.4-7.41). Controlling for age and duration of illness, the PD cohort living in institutional were also more likely to be demented (RR 2.7 (95% CI 1.21- 5.76). In contrast to the PD cohort, the control decedent's place of death was more likely to be in hospital (RR, 1.97, 1.48-2.62).

As a primary or underlying cause of death, dementia was underreported on both the PD and control certificates. Although 144/158 (91%) of the PD cohort had a diagnosis of dementia before their deaths, it was reported in only 14/144 of certificates. Similarly, only two of the control cohort had dementia recorded anywhere as a primary or underlying cause of death. Upon review however, a further four at the time of death had a confirmed diagnosis of dementia.

Discussion.

This investigation reports the cause of death recorded on the death certificates of PD and age matched control cohorts in Denbighshire in the UK. We have previously reported that the life expectancy and average age at death in this PD cohort is much lower than the general population. [16] In the current study the overall SMR for our PD cohort was 1.82, indicating an excess mortality. This is similar to previous investigations where the SMR has been reported to range from 0.9 to 3.8 [16] However, recent community based incident cohort and incident clinical cohort investigations have reported lower SMR's of 1.29 (95% CI, 0.97-1.61), and 1.39 (95% CI, 1.10.-1.50), suggesting a moderate increase mortality compared to the general population. [16,52] The shorter duration of PD diagnosis, lower number of recorded deaths and shorter follow-up period compared with the current investigation may partially explain these differences the current and previously reported UK investigation. In addition, the other European investigation was limited by the retrospective analysis of a data set from 1978-1998 and recruitment solely from a clinical population.

Overall death certification and clinical research data appear to provide disparate mortality data in PD. Although our PD cohort had confirmed UKPDSBB criteria for probable PD, as a primary cause of death (Part 1a), it was recorded in just in over 4% of the cohort. A further 30% had PD recorded in parts 1b and c of their death certificates, and on Part II of certificates it was recorded in a further 19% of cases. Overall, PD was not cited anywhere on 47% of the death certificates, which falls approximately midway with previous certification studies of between 14–70%. [16,34-38] The disparity reported between studies is most likely evidence of the differing methodologies employed such as, populations drawn from pharmaceutical trials alone, clinical samples, or retrospective case or chart record analysis.

Pneumonia was the most cited primary cause of death (52%), in the current study. This observation has also been frequently reported in other investigations. [16,52] Patients with PD, particularly as they become frailer with the progression of their illness, are at greater risk for pulmonary complications, due to obstructive ventilation dysfunction, upper airway dysfunction, and weakened strength of respiratory muscles. [53-55] The most frequently reported other causes of death were cardiovascular disease (21%), cerebrovascular disease (8%) and malignancy (6%).

This is the first study to our knowledge to describe underreporting of dementia as a primary, or underlying cause of death in a community based PD cohort. We have previously reported in this cohort the high prevalence of dementia of around 90%. [56] Upon review of the decedents death certificates, we found that less than 10% had any mention of dementia as an immediate or underlying cause of death. Previous general population investigations have also shown that rates of certification mentioning dementia as a main or underlying cause of death have been consistently under

reported. [57-61] This perhaps is because death certification tends to focus upon the immediate cause of death and does not really capture the multiple factors that contribute to death, particularly with elderly individuals with multiple co-morbidity.

This investigation found that the PD cohort were more likely than the controls to be living in a long term care setting before death. This may be a reflection of the duration, nature and the type of burden PD places upon relatives, especially those who have physical frailty themselves. Caring within the home setting may therefore become impracticable and thus possibly precipitates entry into institutional care. The proportion of deaths in long term care amongst the PD cohort was also significantly higher than the control cohort. A recent study reported wide variations in the place of death of people with PD throughout the world, concluding that individual preference, social and socioeconomic circumstances; cultural, organisation and provision of health and palliative care all contribute to some extent the place of death. [62]

In common with previous mortality investigations, we found fewer recorded cancer deaths within the PD cohort. [63] We did not observe differences in the current or past smoking history frequency between our cohorts. Similarly, no differences were revealed between the cohorts and cancer risk in those who had never smoked. There were no differences seen in the types of cancer type on death certificates compared to smokers and non-smokers. However, in the current smoker groups, significantly more in cancer associated deaths were recorded in the controls compared to the PD cohort. A possible explanation for this disparity may be that mutations of the PARK2 (Parkin) gene found in 6-8% of PD patients, may act in some cancers as a tumour suppressor proteins. [64] The absence or mutation of the Parkin gene is found in several tumour types, suggesting that the mechanisms of cell death in PD may play a role in the inhibition or formation of some cancers. [64,65] The decreased risk of mortality from cancer has also been reported in other neurodegenerative disease including Alzheimer's, Huntington's disease and in populations where mild to moderate with cognitive impairment has also been observed. [66-69] Further studies are needed to explore the associations, risks, possible genetic markers and underling mechanisms in PD and other neurodegenerative conditions, to improve and identify and understand the role of cell death and its decreased cancer risk.

We would caution the message often given to PD patients that they die with, rather than die of the condition. The non-motor features of PD such as dementia and autonomic dysfunction are frequently observed in all stages of the disease and most likely make a significant contribution to mortality.[70] One recent investigation reported that autonomic dysfunction and dementia in PD was predictive of increased mortality particularly in patients with orthostatic hypotension (OH).[71] Another meta-analysis which explored the association with OH and mortality in general populations also concluded that OH may confer a greater risk (RR, 1.40) for mortality. [72] The association between the non-motor

features of PD disease and mortality needs further research to understand and determine if these are causal or not.

This study's strengths are the robust follow-up over an 18-year period of a community based cohort all of whom fulfilled criteria for PD and diagnostic re-evaluation was reviewed regularly over this period to ensure diagnostic accuracy. The repeat measure design of the study also allowed us to control for demographics, and motor and non-motor symptomatology. The limitations of the study are that the PD cohort had a mix of prevalent and incident cases, thus possibly over estimating the possible causal associations with mortality. However, controlling for prevalent and incident cases in our analysis did not reveal any between group significant differences. Our control cohort was selected carefully in terms of age, gender, and disease exposure and may not representative of the general population. We endeavoured to reduce this potential bias by randomly selecting controls from general practitioner lists within defined catchment area as the PD cohort. However, excluding controls with known neurological, psychiatric illness and possibly healthier general health may be a potential source of error. The ideal comparison group in a cohort study would be the same as the cohort of interest, except that they would not have the condition under investigation. In older populations, the selection of any control group is often a compromise in ensuring that the control group differs enough with respect to the condition of interest, yet are similar as possible to explore what other factors influence the outcome under investigation. We believe that our selection of controls without neurological or psychiatric disease allowed us to control for confounding factors in the analysis in both cohorts that would not have been possible in the general population.

Conclusions.

In light of our findings, we feel that the current methods of capturing the cause of death from certification alone significantly underestimate the true population burden of PD. The under reporting of dementia as an underling cause of death in this cohort in addition to PD, also suggests that the interpretation of and quality of mortality data currently is not a valid or reliable source of data. Furthermore, we would admonish the use of mortality statistics alone to plan for future service provision in this patient population.

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Figure legend:

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts.

Table 1:
Demographic and clinical outcomes (Means, *standard deviations)* of the PD and control cohorts

	Parkinson's disease	Control	*p< 0.05*
Gender (female %)	44%	41%	NS
Age (entry into study)	74.2 (8.6)	74.8 (6.6)	NS
Age at death	80.7 (*7.1*)	81.9 (*6.3*)	NS
Institutional care %	52%	30%	0.003
Place of death(Hospital)	37%	74%	0.002
GDS-15	5.6 (2.2)	3.7 (1.1)	0.001
EQ-5D (Weighted health)	0.58 (*0.36*)	0.79 (*0.28*)	0.001
EQ-5D (VAS %)[1]	55 (*16.5*)	77 (*17.6*)	0.001
Onset of PD	67.3 (*10.7*)	------	-----
Duration of PD	13.2 (*8.8*)	------	-----
UPDRS (motor section)	27.9 (*11.7*)	------	-----
H & Y	2.9 (*0.74*)	------	-----
PADL	3.1 (*1.1*)	------	-----

[1] VAS = EQ-%D Visual analogue scale

Table 2.

Primary cause of death (Part 1a death certificates) reported for the PD (n =158) and control (n =34) cohorts.

	Parkinson's disease	Control
Pneumonia	84 (53.2%)	6 (17.6%)
Cardiac	33 (20.9%)	9 (26.5%)
Cancer	10 (6.3%)	8 (23.5%)
Cerebrovascular	12 (7.6%)	4 (11.8%)
Parkinson's disease	7 (4.4%)	0
Other*	12	7

* Other includes, Sepsis; Dementia; Immobility; Chronic obstructive pulmonary disease; Old age; Fracture neck of Femur; Multi-organ failure; Motor Neurone disease.

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Patient consent: All participants gave their informed and written consent on participation.

Data sharing statement: No additional data available.

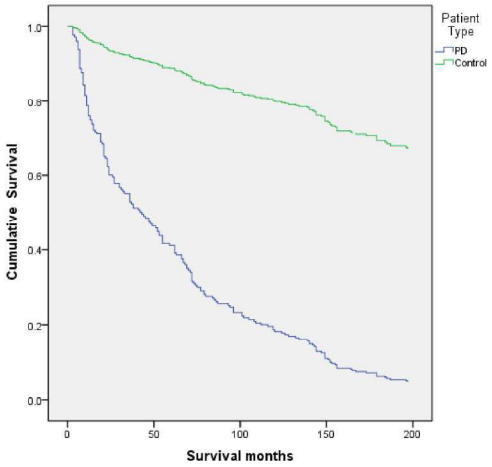

Figure 1.
Kaplan-Meier survival curves for all cause mortality in the PD and control cohorts

297x420mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,6,8
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5.6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	5,6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	5,6
		Cross-sectional study—Report numbers of outcome events or summary measures	--
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,6
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.