PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Hobson, Peter; Meara, Jolyon

VERSION 1 – REVIEW

REVIEWER	Angus Macleod University of Aberdeen, UK
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	This manuscript presents useful data on mortality in PD with novel data on reporting of PD dementia on death certificates. However, there are some major limitations to the way this data is presented and insufficient detail of the methods used. I also think the paper would be helped by clarifying the aims and focusing clearly on these. E.g. adding an aim related to the description of mortality in PD. The paper needs major revision to bring it up to a publishable standard. Specific comments: Abstract 1. Abstract p2 line 16: it is unclear what "Controlling for prevalent PD cases at baseline" means. Please clarify. 2. P2 line 33: I think by "mortality statistics" here you mean specifically mortality statistics derived from death certification. Strengths and limitations 3. The comment "Baseline and subsequent repeat measure data capture allowed analysis for predictive outcomes" adds detail not specified in the methods section. Either remove the reference to repeat measures completely or clarify what this means (? Repeated data collection) and specify details in the methods section. Introduction 4. P3 line 33. The word data is plural so this should read "data are recorded" 5. P3 line 37. Here you give reference to thirteen individual studies. Rather than referencing a subgroup of mortality studies, it would be better to refer to the systematic review of studies of mortality in PD which I have authored (Mov Disord. 2014;29(13):1615-22).

	Methods 6. Details on how patients were recruited and how incident vs prevalent cases were defined are needed. 7. No details are given as to how the controls were selected in the GP practices. This is important as selection bias caused by over-healthy controls is common, and may lead to over-estimation of the differences between patients and controls. This is almost certainly present given the difference between the moderate excess of mortality demonstrated by the SMR and the marked difference between the control and PD survival curves in figure 1, which must be associated with a very high hazard ratio. I suggest for transparency's sake you report the hazard ratio, adjusted for age and sex and comment on selection bias in controls. 8. P4 line 34: "onset age of PD diagnosis". This should be either onset age or age at diagnosis as these are different. 9. P5 line 14: "The expected numbers of deaths were calculated using the published UK age- and sex-specific Office of National Statistics (ONS)". This sentence is incomplete. 10. Was the SMR calculated using calendar-year specific mortality rates? Or was the SMR calculated using mortality rates for a single calendar year despite a 17 year follow-up period? Do the authors have any data on whether the Denbighshire mortality is comparable to the national UK mortality used as the comparator for the SMR? 11. Please specify more details of Cox regression including (i) the covariates studied; (ii) which time-dependent variables were studied; (iii) whether proportional hazards assumption was satisfied; (iv) what model-building strategy was used. 12. There is no statement regarding ethical approvals in this paper. This must be added. Results 13. Need baseline characteristics PD vs controls. 14. No data is given re losses to follow-up. This is essential for a cohort study. 15. No data is given re missing data. Please add. 16. P5 line 44: I don't understand what "comparing prevalent and incident cases survival" means. This sounds like a ratio between prevalent and incident cases, but the given ratio does not fit with the statement this is non-significant not with the p-value of 0.186. 17. There is selective reporting of hazard ratios from the Cox regression analysis of predictors of mortality. This should be in a table with all the predictive factors studies. 18. P6 line 3: cohort certificates should be PD certificates (to distinguish from controls in cohort). 19. P6 line 7-8 ". . . cause . . . was . . ". should read ". . . causes . . . were . . ."

	20. P6 line 20: “Disease progression within the PD cohort was significantly associated with a worsening HRQoL at death”. It is unclear (i) how disease progression was measured and (ii) how you could have HRQoL measurement at time of death in these patients. Please explain what you have done in the methods and clarify this statement about QoL at death. 21. P6 line 38: the methods of the review of control patients should be detailed in the methods. Discussion 22. P6 line 52: the range of SMRs is much wider that you have stated here, as you highlight in the next sentence anyway. Again you are selectively quoting the literature. Several studies have SMRs around 1, and others above 3. Quoting the systematic review here would be preferable. 23. P7 2nd para. No need to repeat detailed results in the discussion. 24. P7 line 25. It isn’t clear what has been frequently reported – is it pneumonia as the most cited cause or is it the threefold increased risk? Please rephrase. 25. P7 line 48-50: “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 is an interesting result, but the discussion is not the place to introduce new results. Either remove, or describe in methods and detail the results appropriately in the results section. 26. P7 line 57: The sentence beginning “In contrast . . .” belongs in the results, and not in the discussion. Table 27. The table needs descriptors e.g. mean (SD) etc. 28. Please present data of age at recruitment, to allow comparison of matching of controls on age, which is the strongest risk factor for mortality. Figures 29. Please provide clear and meaningful axis titles e.g. survival probability on y axis and remove the zeroes after the decimal points in months on the X axis. 30. Figure 1 and figure 2 show that nearly 20 percent of patients died at exactly 60 months. This is clearly an error. General points: 31. Many of the results are not directly related to the stated aim. Either expand the aim or focus the other sections more clearly. 32. Providing z-scores together with P-values is unnecessary. Just p-values is fine. 33. Several p-values in the text use < or > instead of =. E.g. P < 0.003 presumably should be p = 0.003. Likewise p< 0.186. 34. I think the referencing is excessive.

	35. It appears the authors think PD should always be included in a death certificate. If a patient with early PD dies from MI it is unlikely that PD contributes to the death and therefore in my view doesn't have a place on the death certificate. While this issue doesn't detract from the message that death certificate data are useless for identifying PD for epidemiological research, perhaps they still identify most deaths related to PD? I think this issue deserves some discussion and if would be interesting to see whether deaths likely to be related to PD e.g. pneumonia were more likely to have PD on the death certificate that those due to e.g. cancer.

REVIEWER	David Oakes University of Rochester, USA
REVIEW RETURNED	24-Aug-2017

GENERAL COMMENTS	This manuscript presents data on a community study of mortality in PD patients. Primary and underlying cases of death were abstracted from deaths certificates obtained over an 18 year follow-up period in the cohort compared with age and gender-matched controls. There was a very substantial excess of deaths among the PD subjects, but PD was often not mentioned on the death certificates, and contributory factors, such as dementia, which were known to be present, often went unmentioned also. The analysis suggests that reliance on information on death certificates would result in major understatement of the role of PD and associated conditions as risk factors for mortality. The authors have several earlier publications on this cohort. It would be useful to see how the additional follow-up reported here has changed conclusions from earlier work. Some methodologic details are lacking from the present paper, perhaps these were reported earlier, but they could bear repeating. My main concern is with the choice of control group. It is stated that this group was screened for several conditions including "parkinsonism, Alzheimer's disease, history of stroke and any other neurological or neurocognitive disorder". Does this mean that any of these conditions would lead to exclusion from the control cohort? If so, one would expect this cohort to be healthier and to live longer than the PD cohort, possibly for reasons unrelated to PD. In fact the control cohort does not add a lot to the primary findings of the paper, the big difference in overall mortality between the PD and control cohorts makes secondary comparisons, such as age or Quality of Life at Death problematic, since one is comparing essentially the entire PD cohort with a subset of the control cohort. Several comparisons are made between "incident" and "prevalent" cases, but it is not clear how these categories are defined. The brief description on page 4 seems to suggest that only prevalent cases were included in the cohort. Summary baseline data should be presented separately for incident and prevalent cases. Presumably the incident cases were younger and less impaired at entry than the prevalent cases, and these differences would strongly influence comparisons between groups. The paper includes discussion of the effect of disease progression and rate of worsening of motor symptoms on mortality.

	The authors should provide specific information about how these analyses were performed. It is invalid simply to divide the cohort into fast progressors and slow progressors based on their entire follow-up history and examine the mortality of each group separately. A landmark analysis can be used in which the follow-up period is divided into an initial period used to classify progression rates and a second period used to assess mortality within each of the groups defined in the first period. Or a time-dependent covariate can be used in a Cox analysis, but if so full details of the specification of the model should be presented. In the discussion of the cancer deaths on page 8 I was surprised to see no mention of the possible effect of the reduced rate of cigarette smoking among PD patients. Page 3, line 48 “trials”

VERSION 1 – AUTHOR RESPONSE

Reviewers 1 & 2:

Abstract: Revised & corrected.

Strengths & Limitations: This section is clarified in the methods section as requested. In addition we have also revised this section for greater clarity.

Introduction: Corrections, revisions (Aims) and reviewer suggestions made.

Methods: This section has been completely revised. All corrections and reviewer suggestions have been incorporated into the manuscript.

Results: We have addressed the issues raised by the reviewers concerning the “prevalent and incident case.” This section has been edited to reflect this.

Other revisions suggested have been incorporated into the manuscript.

Discussion: All suggested revisions are outlined with MS tracking.

Table: Descriptors and the PD and Control cohorts’ age of entry into the investigation have been added.

Figures:

Figure 1: Has been corrected.

Figure 2: This table has been removed because of the issues raised about prevalent and incident cases by the reviewers (addressed in the Methods and Results sections).

General points: We believe that we have addressed the general points raised by the reviewers with the revisions made to the manuscript. We have also reduced the number of references from 84 to 72 as suggested by reviewer 1.

VERSION 2 – REVIEW

REVIEWER	Angus Macleod University of Aberdeen UK
REVIEW RETURNED	06-Oct-2017

GENERAL COMMENTS	The manuscript is much improved. The only substantive issue is the lack of any description of the testing of the assumptions of Cox regression. The following comments are only cosmetic: 1. P3 line 48: typo (trails should be trials) 2. P3 line 25: word missing 3. Fig 1: change CumSurvival (y-axis title) to “Cumulative survival” Fig 2+3: these data could be displayed more parsimoniously in one table with columns for patients and controls

REVIEWER	David Oakes University of Rochester, Rochester NY
REVIEW RETURNED	22-Oct-2017

GENERAL COMMENTS	I was disappointed by the absence of a point by point response to the earlier reviews. The authors recognize that the elimination of some co-morbidities may have biased the choice of control group, but this point deserves further discussion. I continue to believe that the oft-reported inverse association between tobacco smoking and PD may explain most of the deficit seen in cancer deaths in the PD group, this point should be discussed. The overall message of the paper, that one cannot rely on causes of death reported on a death certificate in analyzing the mortality risks associated with PD, is well supported by the detailed analyses of the PD cohort.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

We asked an epidemiologist in Bangor University clinical trials unit to review the statistical robustness of the manuscript (blindly). They were happy with the reporting of the statistics however, they suggested that the lack of a description of the testing of the assumption of Cox regression needed to be clarified as suggested by Dr Macleod. We have now addressed this in the statistical section of the methods.

Typos etc addressed.

Title page and word count added.

Reference number 38 cited.

Figures 2 & 3 have been removed and replaced with a Table.

Reviewer 2:

Please accept our apologies for not giving a point by point response.

We have discussed the choice of control group as requested.

We re-examined and analysed our data with regards to smoking and cancer risk. We have added a section in the results and discussion.

VERSION 3 – REVIEW

REVIEWER	David Oakes University of Rochester Medical Center, USA
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	Thank you for addressing the question of the possible effect of tobacco smoking on mortality in the PD and control groups. This revision is also clearer about the lack of baseline comparability between the PD and control groups. Unfortunately some of the added text on page 26 (tracked version) describing the Cox model is incorrect. Proportionality of hazards does not correspond to parallel survival curves but to parallel log(-log survival) curves. And it is not clear what is meant by "residuals" in this context, several different kinds of residuals can be defined for the Cox model. This inserted text needs to be rewritten, or deleted.

VERSION 3 – AUTHOR RESPONSE

Reviewer 2 requests:

We have taken advice from a statistician and edited and addressed the text in the methods section as suggested by the second reviewer.

Editorial requests. 19/12/17

Figure 2 has been removed from the text and replaced with Table 2.

Manuscript Title, matched in the main document & Scholar One system.

Reference #38 cited properly

Editorial requests. 20/12/17

Table 3 text has been removed