Author's response to reviews

Title: Self-reported parkinsonian symptoms in the EPIC-Norfolk cohort

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Author's response to reviews: see over
Reviewer’s report 2
Self-reported parkinsonian signs in the EPIC-Norfolk cohort

Title: Self-reported parkinsonian signs in the EPIC-Norfolk cohort

1 11 April 2005 Version: Date:

Peter Hobson Reviewer:

Reviewer’s report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Review: Ishihara et al

Self-reported parkinsonian signs in the EPIC-Norfolk cohort.

This is an interesting paper that reports the Self-reported parkinsonian signs in a sub-cohort of the EPIC-Norfolk cohort. Overall the paper is well written, however there are several omissions of references and some inaccuracies that would need to be addressed.

Major Compulsory Revisions

Introduction

Paragraph 1 lines 6 & 7: The authors should reference the papers here. [I have added references here.]

Paragraph 3 line 4. Whilst reduced olfactory function (OF) has been associated with preclinical PD, the authors should also consider that several other conditions such as vascular disease have associations with OF. [I agree with the reviewer’s statement and I have added the statement “although it is not specific to PD”, rather than explaining in detail.]

Methods (1).

Paragraph 2. I am not sure what table 1 contributes to this manuscript. I would suggest that they analyse the longitudinal data or remove this table, because in its present form it appears to be taking up space. [We do not at this time have the date of diagnosis available so cannot do longitudinal analysis. The point of the table was to display the basic characteristics of the total cohort vs sub-cohort. I have removed the middle two columns and added a column for non-respondents so the characteristics can be compared.]

Data analysis

The authors need to describe and name the statistical tests in this section. [I have added the Chi-square test for trend was used in STATA. I had originally used nptrend but have re-analysed since this test is not as commonly used.]

Discussion study population.

Paragraph 1. Whilst I agree that PD is a relatively rare disease in individuals under the age of 45 years, the same cannot be said of those aged over 75 years. PD and parkinsonism is a disease of the elderly and it rises significantly with age and thus it is likely that the although the cohort here may be representative of those aged 45-74 years, it is not representative of a general population and overall it weakens the study because of this selection bias. [We agree that the cohort is healthier, younger than the general population. This is discussed in more detail and at the recommendation of Reviewer3, we have calculated the expected number of PD cases from Schrag et al. 2000 prevalence survey in England]]

Methods (2)

Paragraph 2. The authors in their literature review have missed a number of references such as Mutch et al, (neuroepidemiology 1991), De Rijk et al (neurology 1995), Meara et al (Jrn Epid & Community Health 1997) and a more recent paper 2000 publishes in the JNNP. [References have been added. This study was not meant to be a screening
study or a validation of the screening instrument, since the outcome was self-reported PD and we have not been able to confirm the diagnoses. However it is agreed that the screening questionnaires in the literature do provide comparisons for the responses to questions about parkinsonian symptoms.

Paragraph 3. The authors refer to reference 20 as evidence of misdiagnosis, which would be fine if the current study was a clinico-pathological based study, which it is not. Meara et al, 1999 and Ben-Sholomo et al 2000/1 community based studies are more relevant to the current investigation and should have been referenced. [I have added these references and removed the other reference.]

Discussion
The discussion could be improved if the papers I have already referred to were also compared.
I would suggest that the limitations of the current investigation are discussed in greater detail. [The discussion has been expanded especially with respect to the issue of missing data. We hope that will be sufficient.]

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
Unable to decide on acceptance or rejection until the authors have responded to the

What next?:
major compulsory revisions
An article of limited interest Level of interest: Acceptable Quality of written English: No Statistical review:
Declaration of competing interests:
'I declare that I have no competing interests'

Reviewer's report 3
Title: Self-reported parkinsonian symptoms in the EPIC-Norfolk cohort
Version:
Date: 15 April 2005
Reviewer: Yoav Ben-Shlomo
Reviewer's report:
General
This paper reports opportunistic data from a large and important prospective cohort established to examine associations between dietary intake and cancer. It is at the moment mainly a descriptive paper on the prevalence of parkinsonian symptoms by age and compared to subjects with or without a diagnosis of PD. Such papers are helpful and rarely published as either researchers fail to write up the data and/or journals are less interested in publishing them. In general, such papers should be encouraged but I do have some comments which I feel should be addressed first and which I hope will result in a better and more useful publication. As a small aside I would like to suggest that the authors misuse the term "signs" and in fact mean "symptoms". [A clinician had corrected my original use of "symptoms" and said I should use "signs" instead because they were not all symptoms. I agree that the use of symptoms is more
appropriate so I have changed this.] I may be wrong but I believe that a symptom is a subjective complaint whilst a sign is evidence elicited by a third party (usually a clinician and supposedly more objective) supporting or refuting the presence of pathology. Patients can have symptoms but no signs and vice versa. Sometimes the distinction can be blurred. For example in box 1 bradykinesia and rigidity are signs (you need to undertake passive limb movements to determine if they are present) but difficulty getting out of bed is a symptom. By definition the study is examining self-reported symptoms which we hope are indicative or correlate well with clinical signs. I would suggest the paper is altered to make this distinction. I appreciate that some of the suggestions I have made below will require additional work but I feel that this will make the paper a more useful publication for other researchers to build on.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The authors fail to describe their statistical methods adequately other than state that they used a non-parametric method. They should report exact p-values in table 2 rather than merely having a footnote that all signs are p<0.01. [The non-parametric test for trend (nptrend from STATA) had been used but I have re-analyzed using chi-square tests for trend.] If they feel that the data do show a linear trend with age then they should report the percentage increase (with 95% CIs) for a 10 year increase in age as an additional column to the table. [Not reported because not all symptoms showed a linear increase.] For some reason they do not report the trend values for the combination of signs. [I have removed the part of the Table 2 reporting cumulative number of signs. There were only 2 people reporting all signs. Instead I think the table with sensitivity and specificity provides similar information along with the additional useful information suggested by the reviewer.]

2. They authors should state the follow-up period for obtaining PD diagnosis from hospital and death records since the baseline assessment. [This correction has been inserted into the text: “PD case ascertainment was based on self-report at baseline or 18-month follow-up questionnaire, ongoing reports of ICD-9 diagnosis of PD from computerised hospital discharge records, and ongoing searches of death certificates reports for mention of PD”] Whilst self-reported PD may be specific it would be helpful to check its sensitivity by cross-checking this with reported PD drug consumption. Does the EPIC dataset have medication data? If YES this would be a helpful addition. [The EPIC dataset did collect drug information at the health examination & few (N=29) reported any of the anti-parkinsonian drugs from the British national formulary. It is uncertain whether this is due to underreporting or early/less severe disease. 19 people who self-reported PD had a PD drug reported. 10 individuals not reporting PD had a prescription for bromocriptine or procyclidine but nobody with diagnosed PD reported using these drugs. These two drugs are not specific to PD. I added on sentence about this in the results]

3. One important finding which is not discussed is the high percentage of missing data (40%). It is important to try and understand why this occurred so that future studies can improve on this. I have some concerns about the validity of assuming that missing means absence of symptom. Do the authors have their own thoughts given their large experience in undertaking surveys particularly in elderly populations. Other than age, have they looked for other predictors of missingness e.g. gender, order effect of questions. [A table has been added with a univariate analysis of missingness and
several factors that were thought to contribute to missing data. Comments have also been added. We have not taken the missingness into account for the prevalence reports since it was felt that dealing with the missing data issue is an important but time-consuming process. Possibly it can be a subject for a future EPIC paper. Some subjects may feel that having answered yes already to one or two questions they cannot be bothered to complete the rest. What is the mean number of symptoms in subjects with or without missing having adjusted for age group? How could we do better in the future? I would welcome the thoughts of the authors.

4. The authors discuss the likelihood of a healthy cohort effect. It would be relatively simple and helpful to use the prevalence survey of Schrag et al (BMJ) and calculate an expected number of cases adjusting for age and hence a standardised ratio for cases with and without the self-reported symptoms. This would quantify the potential bias. [The indirect standardization was calculated and an expected number of cases reported in the paper]

5. There was no justification made for why they choose 5 or more symptoms as diagnostic of PD. Other studies have suggested a lower cut-off I believe. [This study was not meant to be an evaluation of a screening questionnaire, and most other studies using a similar questionnaire used it to screen possible parkinsonism and then went on to a second step (clinical exam) to verify the diagnosis. A limited proportion of those who screened positive had PD (low PPV). Reference Chan 2005, Tison 1994 etc. I have excluded this statement.]

6. I had some concerns about the validity of the self-reported symptoms for subjects under 65 years. As the authors point out most previous studies are undertaken in older populations as they are usually part of a door to door survey and hence it is not cost-effective to screen younger subjects. The authors report that only micrographia and walking slower show age related increases which is worrying. It is possible for example that the tremor question is detecting subjects with benign essential tremor who will be younger. The low reported frequency of tremor in the PD cases also makes me worried about this question. The authors argue that the lower prevalence of tremor in their cohort may be due to a selection bias. This is true but it would not explain the low rate amongst cases. Tremor dominant cases are if anything milder than those with more predominant akinetic/rigid presentations. [We agree that tremor-dominant PD is milder than akinetic-rigid forms. Tremor is less prevalent in EPIC PD cases than in other studies. We agree that the tremor question may not be completely specific to Parkinsonian tremor, and that the question was open to participant interpretation. Some other studies asked only about shaking hands or feet and not about if it was “when relaxed” or “when active”. Resting tremor rather than general tremor was used as the symptom definition. If just the tremor question is used then 43 (81.1%) of PD cases and 888 (8%) of individuals with complete symptoms responses answered positively.]

7. The authors should report their search strategy and inclusion/exclusion criteria in the methods section with details of how they undertook their review. I was surprised that for example they did not include the following papers (same project) Screening Parkinson's disease: A validated questionnaire of high specificity and sensitivity Movement Disorders Volume 10, Issue 5, Date: September 1995, Pages: 643-649; J. Duarte, L. E. Clavera, J. De Pedro-Cuesta, A. P. Sempere, F. Coria, D. B. Calne; Field validation of a method for population screening of parkinsonism Movement Disorders Volume 17, Issue 2, Date: March/April 2002. Pages: 258-264

Maria Dolores Sevillano, Jess de Pedro-Cuesta, Jacinto Duarte, Luis Erik Clavera. I am aware of other papers in this area. [The screening papers mentioned have been added for comparison. Originally I was trying to stay away from the idea that this was validating a screening instrument, because we only have self-reported PD and could not
go on to neurological examinations. I can see now that it is useful to compare with the screening instrument and prevalence studies, and to make clear that the current study is different.]

8. I found the discussion of the other papers on the last page of the paper rather difficult to follow. Either they should summarise the study population characteristics in a table or merely highlight possible methodological reasons for discrepancies in their results rather than take us through every study. [The discussion section has been re-written to include the other relevant papers.]

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The authors provide data on the characteristics of subjects who did or did not drop out in table 1 but yet make no comment on these data or provide any results from hypothesis testing [The table has been changed to show the sub-cohort, non-respondents to the 18-month questionnaire and total cohort. Commentary is provided on the differences between the sub-cohort and non-respondents, however hypothesis testing for differences was not conducted. This is because with the large numbers even small differences would be significant.]

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Discretionary Revisions (which the author can choose to ignore)

1. Making the paper more informative. I was surprised that the authors did not present the data on the diagnostic utility (sensitivity, specificity etc) of each symptom and their combinations. Perhaps they intend to submit these results as a separate publication, though given the data in table 2 the reader could calculate the all ages measures themselves anyway. Furthermore I suspect in the absence of a true gold standard (either pathology or examination by a movement disorder specialist) it may be hard to publish such a paper. I would suggest that this paper would be more informative if these data were included as an extra table but this decision must rest with them. [Added in table and description as well as a discussion about the weakness of using only self-reported PD as the outcome.]

Unable to decide on acceptance or rejection until the authors have responded to the

What next?:
major compulsory revisions
An article whose findings are important to those with closely related research Level of interest:
interests
Acceptable Quality of written English:
No Statistical review:
Declaration of competing interests:
No conflict of interest