

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Global Burden of Parkinson's Disease from 1990 to 2021: A Population-Based Study

Authors

Li, Mimi; Ye, Ye; Huang, Zhengping; Ye, Lichao; Chen, Chun nuan

VERSION 1 - REVIEW

Reviewer	1
Name	Kelson, Zoe
Affiliation	University of Exeter, Mathematics
Date	20-Nov-2024
COI	None

With a focus on PD, this study sought to project its burden and trends at the national, regional, and worldwide levels between 1990 and 2021.

Reviewer comments:

"The incidence, prevalence, mortality, DALYs, of PD in 2021 were all higher in men than in women. From 1990 to 2021, the burden in males consistently surpassed that in females, with the gender difference widening as age"

Can statistical results please be reported in support of the study findings in the Abstract?

"The Global Burden of Disease 2021 provided the PD burden data"

Can the authors please further comment on whether the GBD data can be considered to be globally and regionally representative?

Can the authors please comment on completeness, scarcity and missingness of the data?

"Using an ordered set of 1000 drawings, the 2.5th and 97.5th percentiles were used to calculate the 95% uncertainty interval (UI)"

The authors have satisfactorily assessed and communicated uncertainty.

Figures 1-3: Can uncertainty intervals please be plotted in these figures?

"The GATHER Guidelines for Accurate and Transparent Health Estimates Reporting were followed by the cross-sectional study"

Can a copy of the GATHER checklist please be provided?

"ASR was used to calculate the EAPCs using a linear regression model"

and

"regions were categorized into four groups using a hierarchical cluster analysis according to the temporal patterns in the PD ASR etiologies"

and

"forecasted the trends in the PD ASRs from 2022 to 2046 using the Bayesian age-period-cohort analysis (BAPC) model"

appropriate modelling methods

Can the authors please specify the cluster analysis methodology?

Can the authors please report on sex-standardised rates, as well as age-standardised rates?

"The global ASPR of PD was projected to show a continuous upward trend. The ASPR of males and females were projected to be 206.00 per 100,000 and 149.44 per 100,000 in 2046, respectively. The incidence rate of PD in both genders has increased with the ASIRs for the females and males, with populations increasing from 13.60 per 100,000, and 21.72 per 100,000 in 2029 to 15.59 per 100,000, and 24.06 per 100,000 in 2046"

Can uncertainty in these projections (e.g. confidence intervals) please be communicated?

"The study does, however, have a few drawbacks. Firstly, PD is a heterogeneous illness with a range of symptoms, progression styles, and concurrent cognitive deficits[41]. [45]. Because of this, clinicians frequently misdiagnose PD, and a qualified, specialized physician is needed to accurately diagnose Parkinson's disease. The robustness and certainty of our results may have been impacted as a result. Second, we were unable to determine how the various risk variables affected the progression of PD because of the limitations of the GBD study. This emphasizes how important it is to incorporate risk variables into GBD project revisions going forward. Third, future studies should take into account the neurobiological links that we did not mention about the development of Parkinson's disease."

The authors provide a discussion on the study limitations.

Reviewer	2
Name	Hobson, Peter
Affiliation	Betsi Cadwaladr University Health Board, Academic Unit
Date	14-Jan-2025

COI

None

Summary

This is an interesting study that should appeal to neurologists, geriatricians, epidemiologists, service planners and allied health professionals with an interest in movement disorders.

The objectives are clearly stated where the authors aim to project the burden and trends of PD at national, regional, and worldwide levels from 1990 to 2021. The design and methods of the study are appropriate by utilizing data from the Global Burden of Disease (GBD) 2021 data. They employed the age-standardized rate (ASR) and annual percentage change (EAPC) to calculate incidence, prevalence, mortality, and disability-adjusted life years (DALYs). In addition, they employed a Bayesian age-period-cohort (BAPC) model to predict future trends until 2046. The discussion focuses upon the exponential rise in the prevalence and burden of PD globally. The findings emphasise the need for improved control and management strategies for PD, particularly in aging populations. The projected upward trend in PD cases also highlight the need to proactive health policies and awareness campaigns to address this growing public health challenge that PD and Parkinsonism pose, especially in view of the rise of ageing populations throughout the world.

Comments.

1. In general, the quality of English used in the manuscript appears to be fairly good overall, but there are several areas where it could be improved for clarity and grammatical correctness. I am aware that the authors first language is most likely not English and would suggest that it is proof checked and edited by a native English speaker for grammatical, stylistic and typographical errors, which would improve overall readability and additionally improve its quality. I have outlined below some observations:

Consistency in Terminology: Terms such as "age-standardized" and "disability-adjusted life years (DALYs)" are used correctly but can be inconsistent in how they are presented. For example, sometimes "age-standardized" is hyphenated, and sometimes it is not. Consistency in terminology would enhance clarity.

Punctuation and Spacing: There are instances throughout the manuscript where punctuation is missing or improperly placed. For instance, there are spaces before commas and periods in some places that should be corrected.

Sentence Structure: Some sentences are quite long and complex, which may hinder readers understanding. Breaking them into shorter sentences could improve readability. For example, the sentence beginning with "Globally, the overall ASR of the incidence..." could be split for better clarity.

Word Choice: There are a few cases where the word choice may not be the most precise. For instance, "the burden of PD control and management needed to be improved" could be

rephrased for clarity, such as "the management and control of PD need significant improvement".

Grammatical Errors: There are minor grammatical errors, such as subject-verb agreement. For instance, "the gender difference widening as age" should be rephrased for clarity, possibly to "the gender difference widens with age".

Redundancies: Some phrases are redundant, such as "the ASR of incidence and prevalence both increased pronouncedly." The word "both" is unnecessary as it is already implied by "and".

Referencing Style: The referencing style is not consistent throughout the document. For example, the way authors are cited and how citations are presented should be standardized.

2. Statistical analysis: The authors have applied comprehensive statistical data, including age-standardized rates (ASR) and estimated annual percentage changes (EAPC). Although I am familiar with the statistical methods and analysis employed in this study, I feel that a review by an epidemiologist with expertise in statistical methodology is needed to ensure the correct methods and analysis have been applied.

Statistical Analysis P8, Spell out EAPC; last sentence: Line 28-33; Studio and R program, missing references.

3. The manuscript contains several instances of repeated text, especially in the sections discussing the results and methods. For example, some sentences and phrases about the global burden and trends of Parkinson's disease are reiterated in different sections, particularly regarding age-standardized rates, trends by sex, age subgroup, and sociodemographic index.

4. Definitions P8: This appears to have been randomly placed at the end of the methodology section and should have been incorporated into the text at the start of this section. The ICD classification should also have been referenced.

5. The long discussion about the relationship with PD and smoking whilst interesting, is not necessary and should be summarised into one sentence. In addition, the authors outline a weakness of the possible "neurobiological links" with PD, but do not give any examples; this should be addressed and references given.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Comments:

"The incidence, prevalence, mortality, DALYs, of PD in 2021 were all higher in men than in women. From 1990 to 2021, the burden in males consistently surpassed that in females, with the gender difference widening as age"

Can statistical results please be reported in support of the study findings in the Abstract?

Response:

Thank you for your suggestion to include statistical results in support of the study findings in the Abstract. We have now incorporated the relevant statistical values, including incidence, prevalence, mortality, and disability-adjusted life years (DALYs) in men and women, along with the corresponding numerical estimates, to ensure that the findings are adequately supported by statistical results. These additions enhance the clarity and precision of the Abstract while maintaining conciseness.

Comments:

"The Global Burden of Disease 2021 provided the PD burden data"
Can the authors please further comment on whether the GBD data can be considered to be globally and regionally representative?

Response:

We appreciate your request for clarification regarding the representativeness of the Global Burden of Disease (GBD) data. The GBD study integrates multiple data sources, including vital registration systems, hospital records, epidemiological surveys, and modeling techniques, to provide estimates for disease burden at both global and regional levels. Given its standardized methodology and comprehensive approach, GBD data is widely considered to be globally and regionally representative. However, it is important to acknowledge that the accuracy of regional estimates may vary depending on data availability and reporting quality, particularly in lower-income settings where health data collection systems may be less robust. We have now included this clarification in the Methods section to address this point.

Comments:

Can the authors please comment on completeness, scarcity and missingness of the data?

Response:

Thank you for highlighting the importance of addressing data completeness and potential missingness. We acknowledge that while the GBD dataset is one of the most comprehensive sources for global epidemiological estimates, data availability varies across countries and regions. In cases where direct epidemiological data are scarce or missing, GBD employs statistical modeling and imputation techniques to generate estimates. These methods help mitigate data gaps, but it is important to recognize that regions with limited direct data may have wider uncertainty intervals. We have now added a brief discussion on this aspect in the discussion section to provide a more transparent account of data completeness and potential limitations.

Comments:

"Using an ordered set of 1000 drawings, the 2.5th and 97.5th percentiles were used to calculate the 95% uncertainty interval (UI)"
The authors have satisfactorily assessed and communicated uncertainty.

Response:

We appreciate your positive feedback regarding our assessment and communication of uncertainty. We ensured that uncertainty intervals (UIs) were consistently reported throughout the manuscript, using an ordered set of 1000 draws to calculate the 2.5th and 97.5th percentiles, following the established methodology of the GBD study. Thank you for acknowledging this aspect of our work.

Comments:

Figures 1-3: Can uncertainty intervals please be plotted in these figures?

Response: Thank you for your suggestion regarding the inclusion of uncertainty intervals in Figures 1-3. While we acknowledge the importance of representing data variability, we have chosen not to add uncertainty intervals to these figures for the following reasons:

Clarity and Readability: The current figures already present multiple trends across different subgroups (e.g., gender, age, and sociodemographic index levels). Adding uncertainty intervals to all lines would significantly increase visual complexity, potentially making the figures less readable and harder to interpret.

Consistency with Previous Studies: Many similar studies analyzing Global Burden of Disease (GBD) data present trends without including uncertainty intervals in their primary trend figures, instead reporting them in supplementary tables. In our manuscript, we have provided the 95% uncertainty intervals in the corresponding result tables (Tables 1 and 2), ensuring transparency of the estimates while keeping the main figures clear and informative.

Focus on Overall Trends: The primary purpose of Figures 1-3 is to illustrate the overall temporal trends rather than emphasize the exact confidence bounds of each estimate. Since we already discuss uncertainty in the main text and supplementary materials, we believe that adding uncertainty intervals to these figures is not essential.

However, if the reviewer still considers it necessary, we are open to further discussing alternative ways to present the uncertainty information while maintaining figure clarity.

Comments:

"The GATHER Guidelines for Accurate and Transparent Health Estimates Reporting were followed by the cross-sectional study"
Can a copy of the GATHER checklist please be provided?

Response:

Thank you for your request regarding the GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting) checklist. In compliance with these guidelines, we have ensured that our study adheres to the principles of transparency and reproducibility in health estimates reporting. We have now included a completed GATHER checklist as a supplementary file, which outlines how each guideline has been addressed in our study. We appreciate your suggestion, as it further strengthens the transparency and methodological rigor of our research.

Comments:

"ASR was used to calculate the EAPCs using a linear regression model" and

"regions were categorized into four groups using a hierarchical cluster analysis according to the temporal patterns in the PD ASR etiologies" and

"forecasted the trends in the PD ASRs from 2022 to 2046 using the Bayesian age-period-cohort analysis (BAPC) model" appropriate modelling methods

Can the authors please specify the cluster analysis methodology?

Response:

Thank you for your comment regarding the cluster analysis methodology. To ensure clarity, we have now provided a more detailed description of the hierarchical cluster analysis approach used in this study. Specifically, we categorized regions into four groups based on the temporal patterns of Parkinson's disease (PD) age-standardized rates (ASRs) using Ward's method with Euclidean distance as the similarity measure. This method was chosen for its ability to minimize intra-cluster variance while maximizing inter-cluster differences, allowing for a more distinct classification of regions based on disease burden trends. We have now included this clarification in the Methods section to enhance transparency and reproducibility.

Comments:

Can the authors please report on sex-standardised rates, as well as age-standardised rates?

Response:

Thank you for your suggestion to report sex-standardised rates (SSRs) in addition to age-standardised rates (ASRs). While SSRs can provide additional insight into sex-specific disease burden, the primary focus of our study is on the age-standardised burden of Parkinson's disease (PD) over time and across different populations. Additionally, in the Global Burden of Disease (GBD) framework, ASRs are commonly used as the standard metric for international comparisons. Given that ASRs already allow for robust comparisons across populations by accounting for age distribution differences, they are widely adopted in global disease burden studies, including those related to Parkinson's disease. Therefore, to maintain clarity and consistency with previous GBD-based epidemiological research, we have chosen to focus on ASRs in the main manuscript. However, if the reviewer strongly recommends including SSRs, we would be happy to provide them in supplementary materials.

Comments:

"The global ASPR of PD was projected to show a continuous upward trend. The ASPR of males and females were projected to be 206.00 per 100,000 and 149.44 per 100,000 in 2046, respectively. The incidence rate of PD in both genders has increased with the ASIRs for the females and males, with populations increasing from 13.60 per 100,000, and 21.72 per 100,000 in 2029 to 15.59 per 100,000, and 24.06 per 100,000 in 2046" Can uncertainty in these projections (e.g. confidence intervals) please be communicated?

Response:

Thank you for your suggestion to include uncertainty estimates in our projections. We acknowledge the importance of transparently reporting the confidence intervals associated with forecasted trends. In response, we have now included the 95% confidence intervals (CIs) for all projected ASPR and ASIR values in the Results section. These intervals were derived from the Bayesian age-period-cohort (BAPC) model, incorporating the posterior distributions of estimated parameters to reflect the uncertainty inherent in future projections. This revision enhances the robustness and interpretability of our findings by providing a clearer representation of the variability in our estimates.

Comments:

"The study does, however, have a few drawbacks. Firstly, PD is a heterogeneous illness with a range of symptoms, progression styles, and concurrent cognitive deficits[41]. [45]. Because of this, clinicians frequently misdiagnose PD, and a qualified, specialized physician is needed to accurately diagnose Parkinson's disease. The robustness and certainty of our results may have been impacted as a result. Second, we were unable to determine how the various risk variables affected the progression of PD because of the limitations of the GBD study. This emphasizes how important it is to incorporate risk variables into GBD project revisions going forward. Third, future studies should take into account the neurobiological links that we did not mention about the development of Parkinson's disease." The authors provide a discussion on the study limitations.

Response:

Thank you for acknowledging our discussion on the study limitations. We recognize the inherent challenges in analyzing Parkinson's disease (PD) burden using GBD data, particularly regarding diagnostic variability, the inability to assess specific risk factors, and the exclusion of certain neurobiological mechanisms. To further enhance the clarity and completeness of our limitations section, we have refined our discussion to more explicitly highlight the potential

impact of misdiagnosis on data accuracy, the constraints of using aggregated GBD estimates without individual-level risk factor analysis, and the need for future studies to incorporate neurobiological mechanisms contributing to PD progression. These revisions strengthen the transparency of our study's limitations while reinforcing the importance of continued improvements in global disease burden assessments.

Reviewer: 2

Comments:

1. In general, the quality of English used in the manuscript appears to be fairly good overall, but there are several areas where it could be improved for clarity and grammatical correctness. I am aware that the authors first language is most likely not English and would suggest that it is proof checked and edited by a native English speaker for grammatical, stylistic and typographical errors, which would improve overall readability and additionally improve its quality. I have outlined below some observations:
Consistency in Terminology: Terms such as "age-standardized" and "disability-adjusted life years (DALYs)" are used correctly but can be inconsistent in how they are presented. For example, sometimes "age-standardized" is hyphenated, and sometimes it is not. Consistency in terminology would enhance clarity.

Response:

Thank you for pointing out inconsistencies in the use of key terms such as "age-standardized" and "disability-adjusted life years (DALYs)." We have now ensured that these terms are used consistently throughout the manuscript, following standard conventions in epidemiological literature. This adjustment enhances clarity and coherence in the presentation of our findings.

Comments:

Punctuation and Spacing: There are instances throughout the manuscript where punctuation is missing or improperly placed. For instance, there are spaces before commas and periods in some places that should be corrected.

Response:

We carefully reviewed the manuscript to correct all punctuation-related issues, including misplaced or missing spaces before commas and periods. These adjustments contribute to a more polished and professional presentation of the text.

Comments:

Sentence Structure: Some sentences are quite long and complex, which may hinder readers understanding. Breaking them into shorter sentences could improve readability. For example, the sentence beginning with "Globally, the overall ASR of the incidence..." could be split for better clarity.

Response:

We appreciate your suggestion to improve readability by simplifying complex sentences. In response, we have revised several lengthy sentences to ensure better clarity and ease of understanding. For instance, the sentence beginning with "Globally, the overall ASR of the incidence..." has been restructured into two separate, more concise sentences. These modifications allow for smoother reading while preserving the accuracy of the information.

Comments:

Word Choice: There are a few cases where the word choice may not be the most precise. For instance, "the burden of PD control and management needed to be improved" could be rephrased for clarity, such as "the management and control of PD need significant

improvement".

Response:

We recognize the importance of precise wording to effectively convey our findings. As per your recommendation, we have refined word choices to improve clarity. For example, the phrase "the burden of PD control and management needed to be improved" has been revised to "the management and control of PD need significant improvement." This change ensures that our intended meaning is conveyed in a clearer and more direct manner.

Comments:

Grammatical Errors: There are minor grammatical errors, such as subject-verb agreement. For instance, "the gender difference widening as age" should be rephrased for clarity, possibly to "the gender difference widens with age".

Response:

Thank you for pointing out minor grammatical inconsistencies. We have thoroughly reviewed the manuscript and corrected errors such as subject-verb agreement. For example, the phrase "the gender difference widening as age" has been corrected to "the gender difference widens with age," which is grammatically correct and more natural in English.

Comments:

Redundancies: Some phrases are redundant, such as "the ASR of incidence and prevalence both increased pronouncedly." The word "both" is unnecessary as it is already implied by "and".

Response:

We acknowledge that some phrases were unnecessarily repetitive, and we appreciate your careful attention to detail. We have now removed redundant wording to enhance conciseness without compromising the accuracy of our statements. For instance, the phrase "the ASR of incidence and prevalence both increased pronouncedly" has been revised to eliminate the unnecessary "both," making the sentence more concise while retaining its meaning.

Comments:

Referencing Style: The referencing style is not consistent throughout the document. For example, the way authors are cited and how citations are presented should be standardized.

Response:

Thank you for highlighting the inconsistencies in the referencing style. We have carefully reviewed and standardized all citations throughout the manuscript to ensure consistency in accordance with the journal's required referencing format. This includes ensuring uniformity in the way authors are cited, as well as the formatting of in-text citations and reference list entries. We appreciate this suggestion, as it has helped improve the clarity and professionalism of our manuscript.

Comments:

2. Statistical analysis: The authors have applied comprehensive statistical data, including age-standardized rates (ASR) and estimated annual percentage changes (EAPC). Although I am familiar with the statistical methods and analysis employed in this study, I feel that a review by an epidemiologist with expertise in statistical methodology is needed to ensure the correct methods and analysis have been applied.

Response:

Thank you for your comment regarding the statistical analysis. We appreciate your acknowledgment of the comprehensive statistical approach used in this study, including age-standardized rates (ASR) and estimated annual percentage changes (EAPC). To ensure the accuracy and appropriateness of the statistical methods, we have carefully re-evaluated our

analytical approach and cross-checked our calculations. We have also ensured that the statistical techniques used are consistent with those commonly applied in similar epidemiological studies. We believe that the methodology is robust and appropriate for assessing the burden and trends of Parkinson's disease, and we appreciate your suggestion, which has encouraged us to further verify the rigor of our analysis.

Comments:

Statistical Analysis P8, Spell out EAPC; last sentence: Line 28-33; Studio and R program, missing references.

Response:

Thank you for your suggestions regarding the Statistical Analysis section. We have now spelled out the full term for EAPC (Estimated Annual Percentage Change) upon its first mention to ensure clarity for readers unfamiliar with the abbreviation. Additionally, we have carefully reviewed the last sentence on Lines 28-33 and made necessary revisions to enhance readability and precision. Furthermore, we have added the appropriate references for the Studio and R program to ensure completeness and proper citation of the statistical software used in our analysis. These revisions contribute to greater clarity and accuracy in our methodological description.

Comments:

3. The manuscript contains several instances of repeated text, especially in the sections discussing the results and methods. For example, some sentences and phrases about the global burden and trends of Parkinson's disease are reiterated in different sections, particularly regarding age-standardized rates, trends by sex, age subgroup, and sociodemographic index.

Response:

Thank you for your valuable feedback regarding the repetition of text, particularly in the methods, results, and discussion sections. We have carefully revised the manuscript to enhance clarity and conciseness:

Methods Section: We streamlined the description of data sources and statistical analyses, ensuring that key methodological details are presented concisely in one place.

Results Section: We reduced redundancy in the presentation of PD burden trends by consolidating overlapping information across subsections. The discussion of ASRs, trends by sex, and SDI regions has been refined to emphasize unique findings rather than reiterating similar trends.

These revisions significantly improve the readability and coherence of the manuscript while maintaining the rigor of our analysis. We appreciate your thoughtful suggestions and believe that these changes strengthen the overall presentation of our findings.

Comments:

4. Definitions P8: This appears to have been randomly paced at the end of the methodology section and should have been incorporated into the text at the start of this section. The ICD classification should also have been referenced.

Response:

We appreciate your suggestion regarding the placement of the "Definitions" section. To improve the logical flow of the methodology, we have now repositioned this section to the beginning of the Methods section, where it appropriately introduces key definitions used throughout the study. Additionally, we have included the relevant ICD classification references to ensure clarity and proper citation.

Comments:

5. The long discussion about the relationship with PD and smoking whilst interesting, is not necessary and should be summarised into one sentence. In addition, the authors outline a weakness of the possible “neurobiological links” with PD, but do not give any examples; this should be addressed and references given.

Response:

Thank you for your feedback regarding the discussion on the relationship between PD and smoking. We acknowledge that this section was overly detailed and have now condensed it into a single concise sentence while retaining the key points. Furthermore, regarding the mention of possible “neurobiological links” with PD, we have expanded this discussion by providing specific examples, including references to mechanisms such as α -synuclein aggregation, mitochondrial dysfunction, and neuroinflammation, which have been implicated in PD pathogenesis. These revisions ensure a more balanced and informative discussion.

VERSION 2 - REVIEW	
Reviewer	1
Name	Kelson, Zoe
Affiliation	University of Exeter, Mathematics
Date	04-Mar-2025
COI	

Many thanks to the authors for responding to each comment in turn, providing clarification, and revising the article where required.

"Thank you for your suggestion regarding the inclusion of uncertainty intervals in Figures 1-3. While we acknowledge the importance of representing data variability, we have chosen not to add uncertainty intervals to these figures for the following reasons:...

However, if the reviewer still considers it necessary, we are open to further discussing alternative ways to present the uncertainty information while maintaining figure clarity."

Reviewer request:

The rationale provided by the authors for not amending the plots is appreciated.
Can the authors please show uncertainty on Figure 1, as this should not impact clarity of the plots?
Perhaps individual plots showing uncertainty for each group can be shown in the supplementary material for Figures 2 and 3?

VERSION 2 - AUTHOR RESPONSE

Reviewer: 1

Comments:

Many thanks to the authors for responding to each comment in turn, providing clarification, and revising the article where required.

"Thank you for your suggestion regarding the inclusion of uncertainty intervals in Figures 1-3. While we acknowledge the importance of representing data variability, we have chosen not to add uncertainty intervals to these figures for the following reasons:...

However, if the reviewer still considers it necessary, we are open to further discussing alternative ways to present the uncertainty information while maintaining figure clarity."

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Can the authors please show uncertainty on Figure 1, as this should not impact clarity of the plots?

Perhaps individual plots showing uncertainty for each group can be shown in the supplementary material for Figures 2 and 3?

Response:

We appreciate your positive feedback regarding our assessment and communication of uncertainty. We have showed uncertainty on Figure 1. Meanwhile, in the supplementary material, Figure S1 and S2 showed the uncertainty for Figures 2 and 3.
