PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Burden of visual impairment associated with eye diseases: an exploratory survey of 298 Chinese patients
AUTHORS	Guan, Xiaodong; Fu, Mengyuan; Lin, Fanghui; Zhu, Dawei; Vuillermin, Daniel; Shi, Luwen

VERSION 1 – REVIEW

REVIEWER	Serge Resnikoff BHVI and SOVS, University of New South Wales, Sydney, Australia
REVIEW RETURNED	19-Apr-2019

GENERAL COMMENTS	The authors are to be congratulated for addressing an issue that is of particular public health importance, especially in the framework of universal health coverage. There are however a couple of issues that need to be addressed: - although the title clearly spells out that the paper is about (economic) burden in two tertiary hospitals in Beijing, which is perfectly right, the text in the body of the article refers to China. This gives the impression that the authors infer generalisation of findings to the whole China when the sample is not representative of any population. This should be addressed throughout the paper (see specific comments below). - the paper claims to assess the economic burden of vision impairment (VI). However, the results actually report the burden associated to the morbidity leading to VI - i.e. the diseases such as cataract, glaucoma etc. - rather than the economic burden related to the limitation of the body function, i.e. the impairment. Language in the paper should be adapted to reflect the actual burden that is assessed. For example, the health insurance is covering (or not) out-of-pocket expenses that are related to the investigation, treatment and follow up of eye diseases rater the expenses related to the inability to see. In other words this paper is primary about the economic burden of severe eye diseases leading to VI and blindness. - all eye conditions (cataract, uncorrected refractive errors, glaucoma, diabetic retinopathy...) are lumped together. The issue here is that these disease are very different: some are treatable in a short period of time (cataract and refractive errors) while others are irreversible. Some require constant treatment (e.g. glaucoma) while other need surveillance and treatment on demand (e.g. diabetic retinopathy or AMD). The management of these diseases is therefore completely different and analysing them as a single group is not appropriate. The authors are therefore strongly encouraged to analyse data by specific disease, with some possible groupings if some diseases are very rare. At the

minimum, cataract, refractive errors, glaucoma and DR should be analysed separately.

Specific comments:
Page: 3
L 32: shouldn’t this be average direct cost?

L 39: “in Beijing” rather than “in China”

Page: 5
L 72 If the objective is to assess the situation in China, then the sample should have been representative of the Chine population, which is clearly not the case here. Recommend replacing China by Beijing throughout the paper.

Page: 6
L 86 Are you referring here to the level of vision impairment (moderate, severe, blindness) or to the condition (i.e. the disease) that is leading to VI such as cataract, glaucoma, DR etc.? If it is the former, then I recommend replacing "visual condition" by "level of vision impairment" to avoid any confusion.

L 87 Is this visual condition or visual impairment ?

L 91 Suggest clarifying from the outset than it was about out of pocket expenditures only.

L 95 Please explain why that specific method was selected to measure QoL?

L 107 This section needs to be expanded to clarify how the hospitals were selected and how the participants were actually selected? Any criteria regarding the duration of the VI? How the sample size was determined?

L 112 “two tertiary hospitals in Beijing” Please clarify which ones?

Page: 7
L 149 To what extent observed patients’ characteristics were similar to those of Beijing inhabitants? of Chinese population (this should be also addressed in the discussion)

Page: 8
L 157 What was the distribution of the causes of vision impairment?

L 175 this needs to be stressed as the reported percentages are very low, meaning that eye care is not properly covered by the existing health insurance schemes. It would have been interesting to compare the coverage across the different health insurance schemes by specific eye condition (e.g. coverage of cataract, of glaucoma. of DR…)

L 186 Again, here it looks like it is more about the economic burden of morbidity than the economic burden of impairment, which is perfectly fine but needs to be clearly stated.

L 187 It would be interesting to compare CHE prevalence across the range of causes. It is likely that some causes may more lead to CHE than others.

	Page: 9 L 196 Here again, it would have been interesting to assess if the QoL was more affected by certain causes of VI. L 205 see previous comment about Beijing vs China L 209 Health care costs in the USA are known to be the highest in the world. Is there any additional country that could be used?

REVIEWER	Mercy Mvundura PATH, USA
REVIEW RETURNED	08-Jun-2019

GENERAL COMMENTS	In general, the manuscript lacks key details which would help the reader understand the context and methods used to generate the results that are presented. Specific comments are below. The introduction section should be strengthened to provide some additional contextual background that can help the reader understand the results. For example, information about the different medical insurance coverages and also which services and care related to VI are covered and how these coverages differ by insurance type would be helpful. In addition, some information on median or average income in China versus USA would also be helpful again to help cast the results in the right context. The methods section is weak and lacks key information which would help the reader understand what was done. Especially information on how the expenditure data were obtained are not clear. The authors mention that interviews were done but it is not clear whether medical bills or receipts were obtained from the people interviewed or from their insurers. Or are the expenditures self-reported but based on what source and how were these validated? On page 86 they mention that they asked about health service utilization, treatment history etc. Over what period of time. Where these data collected as quantities if services received and then multiplied with charge or cost data to estimate expenditure? Again, it is not clear what the sources of the expenditure data are. How were treatment costs for comorbidities during seeking outpoint and inpatient care handled? How did the authors ensure that only costs for VI were accounted for? In the results, again it would have been good to provide some context for the reader such as how the different insurance schemes cover different costs associated with VI. This would provide some context for what is reported in lines 156 to 160. Explain more what is included in the direct medical costs reported in lines 169 to 171. Again, how were these data leading to these estimates obtained? In Table 1 it is not clear how the p-values are calculated when there are more than two categories (e.g., for educational level, occupation or age) and yet one p-value is reported. In Table 2, the direct medical costs for drugs in outpatient settings are really high. What is the reason for that? What are they so much higher than even for inpatient care? What types of treatment are they getting to get these costs to be this high? It would be helpful to again provide more context about what treatment the people with VI are typically getting in inpatient and outpatient care and whether this is solely related to VI or other comorbidities.

	Also, the direct non-medical costs, are those related solely to VI or comorbidities? How were escort costs valued?

VERSION 1 – AUTHOR RESPONSE

Response to reviewers' Comments	
Thank you for your suggestions. The two reviews were positive and helpful. After having carefully considered the comments, we have revised the manuscript accordingly. We hope that it read more smooth and the analysis and results will be more rigorous. If there is anything we still need to improve, please let us know.	
Reviewer 1' Comments	Authors' reply
1. Although the title clearly spells out that the paper is about (economic) burden in two tertiary hospitals in Beijing, which is perfectly right, the text in the body of the article refers to China. This gives the impression that the authors infer generalisation of findings to the whole China when the sample is not representative of any population. This should be addressed throughout the paper (see specific comments below).	Thank you very much. The burden of VI has been well researched in advanced economies, however, little is known in China (an upper middle-income country). Therefore, we designed this exploratory study to explore the burden of VI and hoped to give some suggestions to policy makers in China. But the first challenge is to find the VI patients in China. Clinical pharmacists suggested us to conduct the survey in tertiary hospitals in Beijing. The main reason is that patients from all over China come to see doctors in Beijing's tertiary hospitals, which would give us the best chance to find the targeted individuals. After two rounds of experts and physicians' trial interviews — which took into account the length of interview to patients, the volume of patients in the 2 sample hospitals (most ocular outpatient visits) and also the budget (we planned to finish the interviews in one month but actually took three months to conduct) — we aimed to collect at least 300 patients to achieve an explanatory survey to quantify the economic burden, CHE prevalence and QoL of Chinese patients with VI associated with ocular diseases. We apologize for the misunderstanding and we admitted the sample is not representative of Beijing or China, so we modified our title, the way of saying our objective, the related description in Methods, Results, Discussion and Conclusion section to help readers understand.

2. The paper claims to assess the economic burden of vision impairment (VI). However, the results actually report the burden associated to the morbidity leading to VI - i.e. the diseases such as cataract, glaucoma etc. - rather than the economic burden related to the limitation of the body function, i.e. the impairment. Language in the paper should be adapted to reflect the actual burden that is assessed. For example, the health insurance is covering (or not) out-of-pocket expenses that are related to the investigation, treatment and follow up of eye diseases rater the expenses related to the inability to see. In other words this paper is primary about the economic burden of severe eye diseases leading to VI and blindness	Thank you very much for your suggestion. We have made the revisions according to your comments. We defined economic burden in our study as "direct costs related to the investigation, treatment and follow up of eye diseases leading to VI and the expenses related to the vision loss/inability to see in the method section". We also clarified this in the title of the study.
3. All eye conditions (cataract, uncorrected refractive errors, glaucoma, diabetic retinopathy...) are lumped together. The issue here is that these diseases are very different: some are treatable in a short period of time (cataract and refractive errors) while others are irreversible. Some require constant treatment (e.g. glaucoma) while other need surveillance and treatment on demand (e.g. diabetic retinopathy or AMD). The management of these diseases is therefore completely different and analysing them as a single group is not appropriate. The authors are therefore strongly encouraged to analyse data by specific disease, with some possible groupings if some diseases are very rare. At the minimum, cataract, refractive errors, glaucoma and DR should be analysed separately.	Thank you for your suggestion. We agree that the analysis data by specific disease is very important. Therefore, we adjusted the Results section. We added tables, data descriptions as well as discussions regarding different eye conditions (causes of visual impairment). The causes of visual impairment were noted using standard World Health Organization (WHO) methodology for surveys on visual impairment. Available from: http://apps.who.int/iris/bitstream/10665/67896/1/PBL_88.1.pd f .
Specific comments	
4. Page3, L 32 shouldn't this be average direct cost?	Thank you for your comment. We have made the revisions to "Annual average direct costs per patient" as suggested.
5. Page3, L 39 "in Beijing" rather than "in China"	Thank you for your comment. We have made the revisions to "Our study explored the economic burden and QoL of visual impairment associated with eye diseases of Chinese patients".

6. Page5, L 72 If the objective is to assess the situation in China, then the sample should have been representative of the Chinese population, which is clearly not the case here. Recommend replacing China by Beijing throughout the paper.	Thank you for your comment. As we mentioned in our reply to Question 1, we agreed that our sample can not represent the whole of China or Beijing and this is an exploratory study. So we have modified our saying of objective into "we aim to achieve an explanatory survey to: quantify the economic burden; identify the prevalence of catastrophic healthcare expenditure (CHE) prevalence; and describe the QoL of Chinese patients with VI associated with ocular diseases".
7. Page6, L 86 Are you referring here to the level of vision impairment (moderate, severe, blindness) or to the condition (i.e. the disease) that is leading to VI such as cataract, glaucoma, DR etc.? If it is the former, then I recommend replacing "visual condition" by "level of vision impairment" to avoid any confusion.	Thank you for your comment. We have made the revisions to "level of visual impairment" as suggested.
8. Page6, L 87 Is this visual condition or visual impairment ?	Thank you for your comment. We have made the revisions to "level of visual impairment".
9. Page6, L 91 Suggest clarifying from the outset than it was about out of pocket expenditures only.	Thank you for your suggestion. We have clarified in the Economic burden section that the costs in our study included direct medical costs, which were further divided into insurance covered and out-of-pocket parts, and direct non-medical costs.
10. Page6, L 95 Please explain why that specific method was selected to measure QoL?	Thank you for your comment. The time trade-off (TTO) valuation technique is one of the most validated health preference instruments that is commonly used in QoL measurement to understand a patients' perception of their own health. Thus, QoL was weighed by the "utility value" using TTO valuation technique in this study. And we have added relative explanation in the QoL measurement selection.

11. Page6, L 107 This section needs to be expanded to clarify how the hospitals were selected and how the participants were actually selected? Any criteria regarding the duration of the VI? How the sample size was determined?	Thank you for your comment. We have made some revisions in the Recruitment and sampling and Data collection and quality control section. We added the descriptions of the selection of hospitals. Two of the tertiary hospitals in Beijing that accepted most ocular outpatient visits were recruited using convenience sampling methods to collect the samples faster. The duration of the VI was only one of the clinic-related characteristic of the patients for description and not included in the recruitment criteria. We also added how the sample size was determined. Sample size calculations were determined based on the interview of expert and physicians, the length of each planed patient face-to-face interview as well as the volume of VI patient visit per day. We aimed for at least 300 patients. We planned to collect 15-20 participants per day, which would take 3-4 weeks for us to complete the data collection. However, due to the strict standards of patient recruitment in our study (moderate VI or worse in both eyes, VA<6/18), we actually took 3 months to meet our designed sample size.
12. Page6, L 112 “two tertiary hospitals in Beijing” Please clarify which ones?	Thank you for your comment. We have added the name of those two tertiary hospitals in the Data Collection section.
13. Page7, L 149 To what extent observed patients’ characteristics were similar to those of Beijing inhabitants? of Chinese population (this should be also addressed in the discussion)	Thank you for your comment. As we mentioned in reply 1 and reply 6, our study was an exploratory study, which may not represent the whole of China and can not represent Beijing. Therefore, we modified our title, our objective, the related description in methods, results, discussion and conclusion section to help readers understand the nature of our study.
14. Page8, L 157 What was the distribution of the causes of vision impairment?	Thank you for your comment. We have added the distribution of the causes of VI in the Description of demographic characteristics section.

15. Page8, L 175 this needs to be stressed as the reported percentages are very low, meaning that eye care is not properly covered by the existing health insurance schemes. It would have been interesting to compare the coverage across the different health insurance schemes by specific eye condition (e.g. coverage of cataract, of glaucoma. of DR…)	Thank you for your suggestion. Most of the people in China are insured by public medical insurance. However, the insurance coverage is extremely complicated between different insurance types according to different populations, geographic regions (as there are supplement insurances in province or city level), drug/health services, funding levels and hospital levels among others. As we mentioned above, our participants came from all over China. So we did not describe the insurance coverage in detail at first. But we agree with your comment that it is interesting to compare the coverage across different related characteristics. So we added Table 3 to show the reimbursement rate by medical insurance, level and cause of VI, current living place and economic status. We also added discussion about the insurance coverage. The average insurance reimbursement rate of Chinese VI patients in our study was low (26.9%), and there were some reasons that might explain this. First, the reimbursement rate in our study was the percent of the whole year costs that is covered by insurance, which means that deductible, co-insurance, costs above coverage gap and costs beyond reimbursement lists were all not included. Second, many drugs or treatment therapies were not covered by the medical insurance. For example, Razumab and Conbercept which were two effective but expensive drugs to treat AMD, were not listed in the Reimbursement during the survey. The good news is they were included in the national reimbursement list after the national pricing negotiations in 2017.
16. Page8, L 186 Again, here it looks like it is more about the economic burden of morbidity than the economic burden of impairment, which is perfectly fine but needs to be clearly stated.	Thank you for your suggestion. As we mentioned in reply 2, we redefined economic burden in our study as “direct costs related to the investigation, treatment and follow up of eye diseases leading to VI and the expenses related to the vision loss/inability to see in the method section”. We also clarified this in the title of the study.
17. Page8, L 187 It would be interesting to compare CHE prevalence across the range of causes. It is likely that some causes may more lead to CHE than others.	Thank you for your suggestion. Like reply 3 mentioned above, we adjusted the logic of the result section. We added Table 3 and data descriptions to show the insurance reimbursement rate and CHE prevalence differences by causes of visual impairment.
18. Page9, L 196 Here again, it would have been interesting to assess if the QoL was more affected by certain causes of VI.	Thank you for your suggestion. We added Table 3 and data descriptions to show the QoL differences by causes of visual impairment.
19. Page9, L 205 see previous comment about Beijing vs China	Thank you for your comment. As we mentioned in reply 1, reply 6 and reply 13, we modified our saying into “This study provided primary information for the economic burden and QoL of Chinese patients with VI associated with ocular diseases”.

20. Page9, L 209 Health care costs in the USA are known to be the highest in the world. Is there any additional country that could be used?	Thank you for your suggestion. Like you said, it may not be enough if we only compare our result with studies in the US. So we added more study results in Europe and Thailand in the Discussion section.
Reviewer 2' Comments	Authors' reply
Introduction	
1. The introduction section should be strengthened to provide some additional contextual background that can help the reader understand the results. For example, information about the different medical insurance coverages and also which services and care related to VI are covered and how these coverages differ by insurance type would be helpful.	Thank you for your comment. Most people in China are insured by public medical insurance. However, the insurance coverage is extremely complicated between different insurance types targeting different populations, geographic regions (as there are supplement insurances in province or city level), drug/health services, funding levels, hospital levels and different lists. Our participants in this study came from all around China, so it is difficult to describe which services and care related to VI are covered. But we added basic introduction of the insurances listed in our study in the note of Table 1. We also added Table 3 to show the reimbursement rate by medical insurance, level and cause of VI, current living place and economic status. We added more information about the insurance coverage in the Discussion section to help readers understand.
2. In addition, some information on median or average income in China versus USA would also be helpful again to help cast the results in the right context.	Thank you for your suggestion. We added gross domestic product per capita of China and the US in 2015 in the Discussion section. We also compared our results with some other countries.
Methods	
3. The methods section is weak and lacks key information which would help the reader understand what was done. Especially information on how the expenditure data were obtained are not clear. The authors mention that interviews were done but it is not clear whether medical bills or receipts were obtained from the people interviewed or from their insurers. Or are the expenditures self-reported but based on what source and how were these validated?	Thank you for your comment. Our objective of this study is to achieve an explanatory survey to quantify the economic burden, CHE prevalence and QoL of Chinese patients with VI. Therefore, we designed a questionnaire survey to collect the medical and non-medical costs, the household income, health utility value, etc. from the patients. We chose two of the tertiary hospitals that accepted the most ocular outpatient visits of patients, using convenience sampling methods to collect enough samples faster. These hospitals played leading role on diagnosis and treatment of diseases in China, which attracted a huge number of patients all over China. The participants in our study came from all around China, so it was difficult to obtain all their medical bills or receipts. Besides, most of the people in China are insured by public medical insurance which can't provide any patient identifiable information to any researcher. This means that we can not link our participants in any insurance database. Thus, expenditures collected in our study were all patients' self-reported data based on their recall. This could have recall bias, which was inevitable and we put it in the Limitations section.

4. On page 86 they mention that they asked about health service utilization, treatment history etc. Over what period of time. Where these data collected as quantities if services received and then multiplied with charge or cost data to estimate expenditure?	Thank you for your comment. We collected the patients' whole year health service utilization, treatment history and costs in 2015. Outpatient and inpatient visits were collected as quantities if services received and then multiplied with estimated average expense per visit. Self-purchased drug costs and every types of direct non-medical costs were collected as estimated total expenditure in 2015.
5. How were treatment costs for comorbidities during seeking outpoint and inpatient care handled? How did the authors ensure that only costs for VI were accounted for?	Thank you for your comment. We clarified to the patients that we only collect their direct costs related to the investigation, treatment and follow up of eye diseases leading to VI and the expenses related to the vision loss/inability to see in 2015 excluding their costs due to other comorbidities when we conducted the questionnaire survey. And we have rewritten the Economic burden part in the method section to clarify the definition of direct costs in our study. In order to control ascertainment bias, the investigators read all the contents of the questionnaire during the face-to-face interviews to establish that patients with VI could hear and understand the questions. The researcher emphasized to participants that only vision-related costs were to be included after every question in the economic burden section to ensure accurate recording of economic burden. And we have rewritten the Data collection and quality control part in the method section to help readers understand.
i	
6. L156-160 It would have been good to provide some context for the reader such as how the different insurance schemes cover different costs associated with VI.	Thank you for your suggestion. As mentioned in reply 1, we added basic introduction of the insurances listed in our study in the note of Table 1. We also added Table 3 to show the reimbursement rate by medical insurance, level and cause of VI, current living place and economic status. We added more information about the insurance coverage in the Discussion section to help readers understand.
7. L 169-171 Explain more what is included in the direct medical costs.	Thank you for your comment. We had explained what was included in the direct medical costs in the note of Appendix 1. Considering your comment, we added the explanation in the note of Table 2 as well to help reader understand.
8. In Table 1 it is not clear how the p-values are calculated when there are more than two categories (e.g., for educational level, occupation or age) and yet one p-value is reported.	Thank you for your comment. Chi-square test can check the difference between multiple groups of categorical variables. A p value less than 0.05 in our study indicated that there were significant difference of CHE and QoL between the multiple groups.

9. In Table 2, the direct medical costs for drugs in outpatient settings are really high. What is the reason for that? What are they so much higher than even for inpatient care? What types of treatment are they getting to get these costs to be this high? It would be helpful to again provide more context about what treatment the people with VI are typically getting in inpatient and outpatient care and whether this is solely related to VI or other comorbidities.	Thank you for your suggestion. Patients in China purchase drugs (except for drugs used during hospitalization) mainly during outpatient visits. Only a small proportion of people purchase some drugs in the pharmacies for their ocular treatment after the initial diagnosis, which is completely different with the model of health care system in the US. This result in the higher drug expenses in outpatient care. We have added some detailed introduction and contents of all types of direct medical costs in the note of Table 2.
10. Also, the direct non-medical costs, are those related solely to VI or comorbidities? How were escort costs valued?	Thank you for your comment. As we mentioned in reply 5, direct medical and non-medical costs in our study were both only vision-related costs. The escort costs were meals, transport and accommodation encountered by patients' escorts during all outpatient or inpatient visits. We added the method of escort costs calculation in the note of Table 2.
Formatting amendments	
1. Kindly remove all your Appendices in your Main Document and upload it separately under file designation "Supplementary File" in PDF Format.	Thank you for your advice. We have removed all our Appendices in our Main Document and uploaded it separately under file designation "Supplementary File" in PDF Format.
2. Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions: -How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? -How did you involve patients in the design of this study? -Were patients involved in the recruitment to and conduct of the study? -How will the results be disseminated to study participants? -For randomised controlled trials, was the burden of the intervention assessed by patients themselves? -Patient advisers should also be thanked in the contributorship statement/acknowledgements.	Thank you for your comment. As mentioned reply 2 to editor, we added Patient and Public Involvement statement in the methods section. We stated that there were no patients and public involved in the development of the research questionnaire, the outcome measures, the design, recruitment and implementation of the study. The results will be disseminated through scientific journals.

VERSION 2 – REVIEW

REVIEWER	Serge Resnikoff BHVI, Sydney, Australia
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	There is still the need to make clear in this paper that the study population is not representative of Mainland China. It only reflects the situation of patients in Beijing.

REVIEWER	Mercy Mvundura, Senior Health Economist, PATH, USA
REVIEW RETURNED	24-Jul-2019

GENERAL COMMENTS	The authors have adequately addressed the comments I provided in the first round of reviews.

VERSION 2 – AUTHOR RESPONSE

Response to reviewers' Comments	
Thank you for your suggestions. After having carefully considered the comments, we have revised the manuscript accordingly. If there is anything we still need to improve, please let us know.	
Reviewer 1' Comments	Authors' reply
There is still the need to make clear in this paper that the study population is not representative of Mainland China. It only reflects the situation of patients in Beijing.	Thank you for your comment. We totally agree the sample is not fully representative of mainland China. To make it more clear, we added this as one important limitation in the Discussion section.
Reviewer 2' Comments	Authors' reply
The authors have adequately addressed the comments I provided in the first round of reviews.	Thank you very much.