

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	THE ECONOMIC BURDEN OF VISUAL IMPAIRMENT AND BLINDNESS - A Systematic Review
AUTHORS	Köberlein, Juliane; Beifus, Karolina; Schaffert, Corinna; Finger, Robert

VERSION 1 - REVIEW

REVIEWER	Hiratsuka, Yoshimune Juntendo Tokyo Koto Geriatric Medical Center No competing Interests
REVIEW RETURNED	18-Jul-2013

GENERAL COMMENTS	<p>This is an interesting and important review paper assessing the impact of economic burden of visual impairment (VI) and blindness (B). This paper is the first systematic review that uses a standardized quality checklist to assess the economic evaluation of the published literatures. Overall this is a good paper, with fairly straightforward aims and results. There is one clear conclusion. That is VI and B cause a considerable economic burden not only for affected persons, but also their care givers and society at large, which increases with the degree of visual impairment. I think the work is important to general readers, since overall the economic burden of visual impairment in the world is huge, and it should be become widely known in the world. I have no major comments regarding this manuscript, however, as authors provided a critique of the reviewed studies in the manuscript (page 18, line 54), this review itself is relatively descriptively, or high level of aggregation. Some specific comments that deserve adjustment are as follows:</p> <ol style="list-style-type: none">1. Page 2, line 33~& Page 11, line 42~. What is the unit of these numbers such as US\$PPP 12,175-14,029? Is this “per VI person” , “ per population”, or other ? This is very important number, so it should be defined explicitly.2. Page2, line 25 & Page 6, line 10. There is no description of the PRISMA statement in the main text, but described in the abstract. The explanation of the PRISMA statement approach should be described in more detail in the main text.3. Page 11, line 4. In Figure 2, percent of quality aspects fulfilled was relatively lower in definition and specification of cost data. It definitely deserves further comment in the discussion.4. Page 11, line 8. In Figure 3, there are two articles with kappa scores less than 0.4. Can we say if it is acceptable score?5. Page 15, line 8. The readers of the journal are likely to need more of an explanation of dead weight loss.6. Page 11, line 39. The authors have spelled 'meta-analysis' incorrectly.7. Overall, the manuscript should be more analytic with ingenuity.
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	Though I understand the difficulty that the meta-analysis could not be conducted due to the considerable variability in reporting cost aspects related to cost -VI&B studies, if it possible, it would be better to perform an more in-depth analysis.
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REVIEWER	Margaret Lynne Pezzullo Director, Deloitte Access Economics Australia No competing interests
REVIEW RETURNED	24-Jul-2013

THE STUDY	<p>The title of the article refers to severe VI and blindness but in fact the article and its source studies also include mild and moderate VI severity categories.</p> <p>Direct and indirect costs, intangible effects, and visual impairment (VI) severity categories are not well defined. These definitions vary across studies and this complexity should be acknowledged in the article (e.g. different definitions of blindness across countries).</p> <p>In addition, referring to 'direct' and 'indirect' is no longer best practice terminology as different authors include different definitions and sets of costs in direct and indirect categories (e.g. informal care is typically included in indirect costs not direct costs). Rather than using the confused direct/indirect semantics, specifying types of costs by payer is a preferred rubric (see Frick et al reference below).</p> <p>Intangible effects are defined on p5 as loss of wellbeing or quality of life (YLD) when in fact they also include lost years of life from premature death (YLLs) such that the total equals DALYs.</p> <p>It is not clear why economic studies conducted in developing countries were excluded. Given that 369 of the 389 studies were excluded, this is a concern.</p> <p>Costs attributable to VI should be those over and above costs for people without VI. The findings are sometimes confused in presentation, in that sometimes the absolute costs are presented e.g. \$14882-24180 for 'mean annual expenses' (presumably total health system costs?) of blindness, which is twofold the costs for non-blind patients. In this case the difference i.e. the costs attributable to VI are not presented.</p> <p>Deadweight losses are not equivalent to years of life lost (YLL) as claimed on p5.</p> <p>The healthcare payer perspective is not equivalent to direct costs only as claimed on p5 (e.g. the author's definition of direct costs includes informal care which is not paid by healthcare funders).</p> <p>DALYs are not uncommonly ascribed a monetary value, using the Value of a Statistical Life Year. Indeed this is government recommended practice in Australia.</p> <p>Why was 'vision loss' not included in the search terms (p4)? Why were these terms excluded from the second search: 'refractive error', 'uncorrected', 'presbyopia' 'myopia' 'hyperopia'? The value of the</p>
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	<p>second search is unclear as the conditions are not mentioned in the abstract.</p> <p>The claim on p17 that 'Our finding that indirect costs are much higher than direct costs is mirrored by virtually all other cost-of-illness studies... etc' requires a reference.</p> <p>The abstract and results claims 22 studies were included in the systematic review. Table 1 appears to list 20 studies, albeit one has two references (the Canadian study). Appendix 1 suggests 20. Also the charts in appendix 1 only appear to depict 15 studies (e.g. kappa). This lack of quantitative consistency lends a shadow over the results which rely on less clear evidence from source studies. Suggest that the findings are independently replicated prior to publication of the findings.</p> <p>Should also include and refer to the best practice guidance for cost of VI studies i.e. this critical reference: Frick K, Kymes S, Lee P, Matchar D, Pezzullo L, Rein B, Taylor H (2010) "The cost of visual impairment: purposes, perspectives and guidance", on behalf of The Vancouver Economic Burden Vision Loss Group, Investigative Ophthalmology and Visual Science, 51:1801-1805.</p> <p>References 11 and 44 are referred to as 'internationalstandards' and 'existing cost of illness (COI) study guidelines' - however, (11) is just a list of GDP deflators and Bloom et al does not provide standards but simply recommends them. In contrast, the Vancouver group was specifically formed for this purpose and has 7 conclusions about methods for VI COI studies.</p> <p>This study should also be included: Keeffe JE, Pezzullo ML, Nesbitt SJ, Taylor HR (2005) "The Costs of Low Vision and Blindness: Preventing vision loss can save governments money" Cataract and Refractive Surgery Today October:44-46.</p> <p>Also, reference (4), Taylor et al (2006), is not included in the studies reviewed in Table 1, and should be.</p>
RESULTS & CONCLUSIONS	<p>The appendices are unclear.</p> <p>The methods for presenting/categorising costs are unclear.</p>
REPORTING & ETHICS	<p>Checklist specifies areas 'Not done'. Unsure on ethics issues, due to reference omissions as above.</p>

REVIEWER	<p>John Wittenborn Public Health Research Department NORC at the University of Chicago</p> <p>No competing interests.</p>
REVIEW RETURNED	<p>29-Jul-2013</p>

THE STUDY	<p>References are numbered incorrectly, particularly in tables. Please check the reference numbers.</p> <p>An important missing paper is Frick, Gower, Kempen, Wolff. Economic Impact of visual impairment and blindness in the United States. ARch Ophthalmology 2007. 125(4):544-50. This paper is arguably more important than the more narrowly focused Frick 08 paper, and was developed to complement the Rein 2006 paper, and</p>
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	<p>together form the basis for the 2007 report "Economic Impact of Vision Problems" released by Prevent Blindness America.</p>
RESULTS & CONCLUSIONS	<p>Rein et al should be referenced in Table 2 for direct medical costs: Rein et al estimated direct medical costs from AMD, glaucoma, cataract and diabetic retinopathy.</p> <p>Check content in Table 1: I noticed the following under Rein et al "to estimate the societal economic burden and the governmental budgetary impact of the following visual disorders among US adults aged 40 years and older:" but no conditions were listed.</p> <p>Table 6 includes DALYs, but QALY results do not seem to be captured anywhere. Frick 07, which should be included, estimates QALYs. I think loss of well-being (QALYs and DALYs) may deserve their own section.</p>
GENERAL COMMENTS	<p>This appears to be a very well researched literature review of the costs of low vision and eye disorders. I would suggest making the focus of the review more clear; for example the search criteria only included four eye disorders, and did not include uncorrected refractive error. Smith, Frick, Holden, Fircke. "Potential lost productivity resulting from the global burden of uncorrected refractive error" Bul. WHO 2009;87:431-7. includes estimates of URE burden by WHO region.</p> <p>Frick 07 should definitely be included and possibly Wittenborn 2013 if you extend the publication date criteria to 2013. Along with Rein et al 2007, these are complementary studies that sum to a total estimate of the burden of vision problems in the US.</p> <p>While the PPP metric is useful, it would have been even better to include per capita PPP. To do this, you would need to be careful of the population of measure, for example some costs are per person under a certain health coverage plan or only for certain age groups.</p> <p>I believe this paper is suitable for publication after fixing the mis-numbered references and either including, or stating a basis for excluding, Frick et al 2007.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer: Yoshimune Hiratsuka

Comment 1: Page 2, line 33~& Page 11, line 42~. What is the unit of these numbers such as US\$PPP 12,175-14,029? Is this "per VI person" , " per population", or other ? This is very important number, so it should be defined explicitly.

Answer: We clarified the unit of measurement used.

Comment 2: Page2, line 25 & Page 6, line 10. There is no description of the PRISMA statement in the main text, but described in the abstract. The explanation of the PRISMA statement approach should be described in more detail in the main text.

Answer: We explained the PRISMA statement approach in more detail in the main text (see page 4).

Comment 3: Page 11, line 4. In Figure 2, percent of quality aspects fulfilled was relatively lower in

definition and specification of cost data. It definitely deserves further comment in the discussion.

Answer: We have further discussed figure 2 (see page 19).

Comment 4: Page 11, line 8. In Figure 3, there are two articles with kappa scores less than 0.4. Can we say if it is acceptable score?

Answer: We included further descriptions of Kappa values, and the range commonly used to determine acceptable concordance (see section “methods” ◊ “quality of included studies”)

Comment 5: Page 15, line 8. The readers of the journal are likely to need more of an explanation of dead weight loss.

Answer: We have added more information and explain the concept of dead weight losses in the methods section (on page 6). Dead weight loss, also known as an excess burden, is not a clearly defined concept. IN a purely economic sense, deadweight loss described the costs to society created by market inefficiency. In the context of our study we refer to it as an excess financial burden to society caused by visual impairment and blindness.

Comment 6: Page 11, line 39. The authors have spelled 'meta-analysis' incorrectly.

Answer: We have corrected the spelling.

Comment 7: Overall, the manuscript should be more analytic with ingenuity. Though I understand the difficulty that the meta-analysis could not be conducted due to the considerable variability in reporting cost aspects related to cost -VI&B studies, if it possible, it would be better to perform an more in-depth analysis.

Answer: As highlighted by the reviewer, the considerable variability between the studies does not allow for a meta-analysis. As recommended, we have expanded the sections describing the process of our high-level aggregation and its implications.

Reviewer: Margaret Lynne Pezzullo

Comment 1: The title of the article referes to severe VI and blindness but in fact the article and its source studies also include mild and moderate VI severity categories.

Answer: We changed the title to “The economic burden of visual impairment and blindness – a systematic review”.

Comment 2: Direct and indirect costs, intangible effects, and visual impairment (VI) severity categories are not well defined. These definitions vary across studies and this complexity should be acknowledged in the article (e.g. different definitions of blindness across countries).

Answer: We agree that the multitude of different definitions pertaining to costs as well as visual impairment are at times confusing. Our descriptions of costs in section “methods” provides a short overview of the different types of costs which are then detailed in much more depth in Appendix 2, highlighting the very heterogeneous definitions and use of cost categories between studies. In the discussion one of the major limitations highlighted are the heterogeneous definitions of blindness and visual impairment across studies which are often based on the legal cut off for

blindness which differs between countries. As the main focus of the review is on cost, we did not discuss the differing definitions of blindness beyond listing them in table 1.

Comment 3: In addition, referring to 'direct' and 'indirect' is no longer best practice terminology as different authors include different definitions and sets of costs in direct and indirect categories (e.g. informal care is typically included in indirect costs not direct costs). Rather than using the confused direct/indirect semantics, specifying types of costs by payer is a preferred rubric (see Frick et al reference below).

Answer: As highlighted by this reviewer, there is considerable disagreement on cost categories to be reported in cost-of-illness and cost-effectiveness studies. We prefer to use the semantic of Drummond et al. (2005) to enable comparisons with other reviews and cost-of-illness studies, especially across indications, which also use this semantic.

A number of studies do not report cost stratified by payer but only report partially aggregated direct or indirect costs without any detailed specification of single cost components. Against this background we would prefer to stick with the direct/indirect semantics.

Comment 4: Intangible effects are defined on p5 as loss of wellbeing or quality of life (YLD) when in fact they also include lost years of life from premature death (YLLs) such that the total equals DALYs.

Answer: The sentence highlighted was clarified to stress that loss of well being and reductions in quality of life were only mentioned as examples of intangible effects, and now YLL and YLD are both mentioned explicitly.

Comment 5: It is not clear why economic studies conducted in developing countries were excluded. Given that 369 of the 389 studies were excluded, this is a concern.

Answer: Costs and types of costs vary considerably between developed and developing countries, and are not easily comparable. We extended the section on the parameters of the literature search and their justification to encompass this.

Comment 6: Costs attributable to VI should be those over and above costs for people without VI. The findings are sometimes confused in presentation, in that sometimes the absolute costs are presented e.g. \$14882-24180 for 'mean annual expenses' (presumably total health system costs?) of blindness, which is twofold the costs for non-blind patients. In this case the difference i.e. the costs attributable to VI are not presented.

Answer: As neither cost categories, nor definitions of blindness allowed for a higher level of aggregation, we chose to present all results as they were displayed in the original references, stating the unit of measurement for each study

Comment 7: Deadweight losses are not equivalent to years of life lost (YLL) as claimed on p5.

Answer: It was not the intention of the authors to equalise deadweight losses and YLL. We paraphrased the sentence.

Comment 8: The healthcare payer perspective is not equivalent to direct costs only as claimed on p5 (e.g. the author's definition of direct costs includes informal care which is not paid by healthcare funders).

Answer: We paraphrased the sentence.

Comment 9: DALYs are not uncommonly ascribed a monetary value, using the Value of a Statistical Life Year. Indeed this is government recommended practice in Australia.

Answer: DALYs are not ascribed a monetary value in all countries. We rephrased the sentence to reflect that DALYs may be assigned a monetary value.

Comment 10: Why was 'vision loss' not included in the search terms (p4)? Why were these terms excluded from the second search: 'refractive error', 'uncorrected', 'presbyopia' 'myopia' 'hyperopia'? The value of the second search is unclear as the conditions are not mentioned in the abstract.

Answer: We did not include the term vision loss as it yields the same number of references as visual impairment. As we were interested in studies in a developed country setting, we did not include refractive error (or myopia, hyperopia, presbyopia) as it is exceedingly uncommon for someone being visually impaired by uncorrected refractive errors in a developed country. We do agree with the reviewer that it is a potential limitation which we added to the discussion.

Comment 11: The claim on p17 that 'Our finding that indirect costs are much higher than direct costs is mirrored by virtually all other cost-of-illness studies... etc' requires a reference.

Answer: We added a reference to this statement.

Comment 12: The abstract and results claims 22 studies were included in the systematic review. Table 1 appears to list 20 studies, albeit one has two references (the Canadian study). Appendix 1 suggests 20. Also the charts in appendix 1 only appear to depict 15 studies (e.g. kappa). This lack of quantitative consistency lends a shadow over the results which rely on less clear evidence from source studies. Suggest that the findings are independently replicated prior to publication of the findings.

Answer: We reviewed tables, figures and the main text. After inclusion of the study from Frick et al. 2007, which was mentioned by another reviewer 22 studies were included into the review. Cruess et al and Gordon et al were reporting the same study. We therefore described the study only once in table 1. With our assessment tool/quality checklist we assessed all studies dealing with direct or indirect costs, which were in total 16 (studies of Cruess and Gordon were assessed once and the study by Frick et. all was added). Only for these studies Kappa values are available.

Comment 13 and 14: Should also include and refer to the best practice guidance for cost of VI studies i.e. this critical reference: Frick K, Kymes S, Lee P, Matchar D, Pezzullo L, Rein B, Taylor H (2010) "The cost of visual impairment: purposes, perspectives and guidance", on behalf of The Vancouver Economic Burden Vision Loss Group, Investigative Ophthalmology and Visual Science, 51:1801-1805.

References 11 and 44 are referred to as 'international standards' and 'existing cost of illness (COI) study guidelines' - however, (11) is just a list of GDP deflators and Bloom et al does not provide standards but simply recommends them. In contrast, the Vancouver group was specifically formed for this purpose and has 7 conclusions about methods for VI COI studies.

Answer: We add the suggested reference.

Comment 15: This study should also be included: Keeffe JE, Pezzullo ML, Nesbitt SJ, Taylor HR (2005) "The Costs of Low Vision and Blindness: Preventing vision loss can save governments money" *Cataract and Refractive Surgery Today* October:44-46.

Answer: Keeffe et al 2005 did not describe cost of vision impairment and blindness. All cost

components displayed in the article refer to underlying disease, and no levels of visual impairment and/or blindness were reported. To stay conform to our exclusion criteria the study had to be excluded!

Comment 16: Also, reference (4), Taylor et al (2006), is not included in the studies reviewed in Table 1, and should be.

Answer: We did not include this study because it displays only cost of underlying diseases rather than costs related to the level of visual impairment and/or blindness. Essentially, this is the same problem as with the study of Keeffe et al. (2005).

We refer to the appendices in the manuscript and have clarified what they contain. The methods section has been revised.

Reviewer: John Wittenborn

Comment 1: References are numbered incorrectly, particularly in tables. Please check the reference numbers.

Answer: Reference numbers were corrected.

Comment 2: An important missing paper is Frick, Gower, Kempen, Wolff. Economic Impact of visual impairment and blindness in the United States. ARch Ophthalmology 2007. 125(4):544-50. This paper is arguably more important than the more narrowly focused Frick 08 paper, and was developed to complement the Rein 2006 paper, and together form the basis for the 2007 report "Economic Impact of Vision Problems" released by Prevent Blindness America.

Answer: We included the paper in this study.

Comment 3: Rein et al should be referenced in Table 2 for direct medical costs: Rein et al estimated direct medical costs from AMD, glaucoma, cataract and diabetic retinopathy.

Answer: We did only include study results, which display costs of VI&B (specifying the level of visual impairment) and excluded those that reported costs pertaining to underlying ocular disease but did not specify levels of visual impairment.

Comment 4: Check content in Table 1: I noticed the following under Rein et al "to estimate the societal economic burden and the governmental budgetary impact of the following visual disorders among US adults aged 40 years and older:" but no conditions were listed

Answer: Table 1 was corrected.

Comment 5: Table 6 includes DALYs, but QALY results do not seem to be captured anywhere. Frick 07, which should be included, estimates QALYs. I think loss of well-being (QALYs and DALYs) may deserve their own section.

Answer: We add the paper by Frick et al (2007) to table 6.

Comment 6: Frick 07 should definately be included and possibly Wittenborn 2013 if you extend the publication date criteria to 2013. Along with Rein et al 2007, these are complementary studies that

sum to a total estimate of the burden of vision problems in the US.

Answer: Extending the publication date to mid 2013 would necessitate performing a completely new search, which we are unable to perform. Thus we will not be able to include Wittenborn et al (2013) and ask for the reviewer's understanding.

Comment 7: While the PPP metric is useful, it would have been even better to include per capita PPP. To do this, you would need to be careful of the population of measure, for example some costs are per person under a certain health coverage plan or only for certain age groups.

Answer: We used only PPP because in some studies the reference population was not described and it was impossible to elicit any further details from many of the publications. In order to keep it a uniform metric we would prefer to stick with PPP.

VERSION 2 – REVIEW

REVIEWER	Wittenborn, John NORC at the University of Chicago, Public Health
REVIEW RETURNED	19-Sep-2013

GENERAL COMMENTS	My comments on the original review have all been addressed. Thank you again for the opportunity to review this manuscript.
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