

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The economic impact of delirium in Australia: a cost of illness study
AUTHORS	Pezzullo, Lynne; Streatfeild, Jared; Hickson, Josiah; Teodorczuk, Andrew; Agar, Meera; Caplan, Gideon

VERSION 1 - REVIEW

REVIEWER	wolfram weinrebe HFR Fribourg, Switzerland Department of Geriatric Medicine
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	<p>The data presented are well structured and interesting. The sum of cost is considerable. But the message is already part of the common knowledge: delirium is expensive and dangerous. Some critical questions and remarks:</p> <p>Line 65: wrong - delirium has clear diagnostic approach, it's not difficult to diagnose</p> <p>Line 68: why should the knowledge of cost should be more important than the actual knowledge of the morbidity and mortality of delirium?</p> <p>Line 151: wrong - was delirium measured by cost for psychosis treatment? The paper 23 shows data of young people with 2/3 schizophrenia and 10% Psychosis - there are no old patients - there are no data for delirium</p> <p>Line 179: which relationship between dementia and delirium was considered?</p> <p>The costs like loss of wellbeing (which might be hardly measured in patients with existing cognitive decline) might be hard to calculate</p> <p>The mortality rate is very low - if the patients are to 90% hospital patients we should find much more deaths - following Witlox you should find at least 14.000 death due to delirium - but you cite only 900 - the appendix shows an estimation of deaths, was the death rate calculated by follow ups of delirium patients in hospital?</p> <p>What about the kind of delirium, we know that there are differences in treatment and costs</p> <p>The number of delirium derive to 90% of the hospital treatment, so this is not a cost presentation for the entire population (line 254)</p> <p>There are a lot of estimations and some gap of data - The authors are asked to work more on details, it's not sure if we will find really new and true results.</p> <p>Fazit: No recommendation for publication.</p>
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REVIEWER	Wolfgang Hasemann University Hospital Basel, Switzerland
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	<p>The authors have conducted the first study to estimate the economic impact of delirium in the Australian population using cost of illness methodology. The study provides novel insights in economics of delirium, uses a sophisticated methodological approach, provides a fundus of enriched data and it is recommended to be published with minor revision.</p> <p>The main text consists of 5000 words including references and tables. An appendix of 25 pages add tables and explanations to different sections of the article. The structure of the manuscript is consistent and well structured. The language is scientific and clear. The methodology section needs the addition of data collection, data analysis and ethical considerations.</p> <p>Feedback to the sections in detail:</p> <p>Title page – keywords: Keywords are either not Mesh terms nor are they very specific. Please revise</p> <p>Abstract:</p> <p>P2.L12/13 The study is described as a “cost-of-illness study”. This term will not appear in the main text or in the appendix. Instead, cost-of-illness methodology is used. Please be consistent with the expression.</p> <p>P2. L55/56 “cognitive decline associated with delirium and dementia” comes unexpectedly. The expression dementia is mentioned for the first time in the abstract. It should be integrated as well into methods and results section.</p> <p>Introduction</p> <p>P4. L 7/8 There is a mismatch between the expression “often” (see “Delirium is a common, serious, and often-fatal medical condition”) and the mortality rates (hazard ratio 1.77) provided in table 1.5. Please adjust wording.</p> <p>P4. L9/10 Ref [1]. Please refer to a defining society or classification system.</p> <p>P4. L16/17 Inouye (Ref [2]) doesn’t use the expression “impaired cognition”. Please add corresponding reference.</p> <p>P4. L24/25 “nursing time per patient” is not mentioned in Ref [2-4]. Please add corresponding reference.</p> <p>P5. L38/39 Please provide a reference</p> <p>Methodology</p> <p>P6 L5/6 “cost-of-illness methodology” Please provide a reference</p> <p>P6. L 25/26 Please provide an example for “This approach is combined with both bottom-up and top-down approaches to estimate...”</p> <p>P7. L46/47 “attributable fraction approach” Please provide a reference to this method</p> <p>P9. L26/27 “friction cost method” Please provide a reference to this method</p> <p>P9. L57/58 “DALYs” Please provide a reference to this method</p> <p>P10. L3-7 “YLDs” “YLLs” Please provide a reference to this method</p> <p>P10 L31/32 Abbreviation first mentioned: AIHW</p> <p>The following sections are missing: (1) data collection (2) data analysis (statistician? Software?) (3) Ethical considerations.</p>
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	<p>Results: P11. L 20/21 Please provide percentages of the population P12 Table 1: Please provide the numbers and percentages Appendix: P33 Table 1.2 Would it be possible to provide the percentages to the corresponding age group in the population? P44 L22/23 Please "opportunity cost method" provide a reference to this method</p>
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REVIEWER	Virginia Mumford Macquarie University
REVIEW RETURNED	14-Mar-2019

GENERAL COMMENTS	<p>Thank you for asking me to review this cost of illness study on delirium in Australia. This is a timely study and I have a few comments for review.</p> <p>Page 4, para 1 – it might be more helpful to use the DSM 5 definition of delirium – the authors state that delirium occurs within the setting of a medical condition but some forms of delirium occur due to other factors – such as drug use. The definitions used by the authors could be confused with other forms of cognitive impairment, and does not include the element of inattention that forms a critical component of diagnostic testing.</p> <p>Page 4 L55 – the authors should clarify that the studies indicate that delirium is the most common complication for the over 65s and also these studies were done in the Sweden not Australia</p> <p>Page 5 L65 The authors should include the fact that there are validated tools for diagnosing delirium</p> <p>Page 8 L141 It might also be helpful to add the delirium research awards from Dementia Australia</p> <p>Page 15 L270 the authors should qualify that the figures for delirium are their estimates</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: wolfram weinrebe

Institution and Country: HFR Fribourg, Switzerland Department of Geriatric Medicine Please state any competing interests or state 'None declared': none declare

Please leave your comments for the authors below The data presented are well structured and interesting.

The sum of cost is considerable. But the message is already part of the common knowledge: delirium is expensive and dangerous Some critical questions and remarks:

Line 65: wrong - delirium has clear diagnostic approach, it`s not difficult to diagnose

Response: This sentence (page 5, lines 71-73) has been revised so that it calls for understanding of the costs of delirium because delirium is often missed (as noted in the paper in as many as two thirds of cases). We have better reflected that delirium has a clear clinical definition (page 4, lines 47-53 and page 5, lines 73-74).

Line 68: why should the knowledge of cost should be more important that the actual knowledge of the morbidity and mortality of delirium?

Response: The cost of delirium, including the morbidity and mortality of delirium are not mutually exclusive. In this article, we also estimate the costs associated with the morbidity and mortality due to delirium by using the value of a statistical life year, which is based on published government guidance in Australia. That is, we also mean that understanding the costs, mortality and morbidity of delirium are important to prioritise prevention, diagnosis and treatment. However, we have revised the sentence so that it also discusses mortality and morbidity (Page 5, lines 74-76).

Line 151: wrong - was delirium measured by cost for psychosis treatment? The paper 23 shows data of young people with 2/3 schizophrenia an 10% Psychosis - there are no old patients – there are no data for delirium

Response: This paper refers specifically to costs in Australian general practice (which we recognise is likely to be a small proportion of all cases in Australia). The costs related only to organic psychoses, or delusional disorders, which includes delirium. Unfortunately, this is the best available data in Australia, and the costs are inconsequential relative to the overall costs of delirium. There is value in including this estimate as it suggests that more research is needed on the impacts of delirium within the Australian primary care system. We have clarified that it is an assumption (Page 11, line 199).

Line 179: which relationship between dementia and delirium was considered?

Response: Epidemiological studies, and tissue, culture and animal studies, suggest that delirium leads to permanent cognitive decline and dementia (Inouye et al, 2014). Fong et al (2015) establish a number of potential mechanisms linking delirium to permanent cognitive damage and dementia, including:

- neurotoxicity, caused by drugs, anaesthesia, or endotoxins;
- neuronal dysfunction associated with inflammation caused by a surgery or acute illness;
- chronic stress;
- neuronal damage, such as prolonged cerebral ischaemia which may lead directly to cerebral dysfunction through impaired blood flow; hypoglycaemia; shock; or sepsis;
- acceleration of dementia pathology, including altering beta amyloid plaques; and
- diminished cognitive reserve.

We have moved data from our supplementary file that showed the sources used to estimate the attributable fraction between delirium and dementia (Page 13, lines 253-255).

The costs like loss of wellbeing (which might be hardly measured in patients with existing cognitive decline) might be hard to calculate. The mortality rate is very low – if the patients are to 90% hospital patients we should find much more deaths – following Witlox you should find at least 14.000 death due to delirium - but you cite only 900 - the appendix shows an estimation of deaths, was the death rate calculated by follow ups of delirium patients in hospital?

Response: The hazard ratio (1.77) based on data from Witlox et al was applied to general population mortality rates, including the 1.4-fold increase for mortality for people who had delirium, for the respective age groups to estimate the number of deaths associated with delirium in 2016-17. It was expected that 12,571 people who had delirium would die in 2016-17, noting not all mortality is due to delirium itself (e.g. comorbid dementia or other illness may contribute to both delirium and death). Deaths due to delirium were estimated by applying the population attributable fraction to total deaths in the delirium cohort in 2016-17.

The population attributable fraction was estimated using the formula, $PAF = (P \cdot (HR - 1)) / (P \cdot (HR - 1) + 1)$, where P equals the prevalence rate for each age group, and HR equals the hazard ratio. The population attributable fraction is then multiplied by the total number of deaths that occur in people with delirium. On average, delirium caused 7.2% of the deaths within the population. These estimates agree with data from the Australian Bureau of Statistics cause of death data, which found that delirium contributed to 802 deaths as a primary or additional cause in 2014-15 in Australia. The ABS cause of death data were not available for 2016-17, although the two estimates are comparable.

What about the kind of delirium, we know that there are differences in treatment and costs. The number of delirium derive to 90% of the hospital treatment, so this is not a cost presentation for the entire population (line 254). There are a lot of estimations and some gap of data - The authors are asked to work more on details, it is not sure if we will find really new and true results.

Fazit: No recommendation for publication.

Response: There is value in publishing cost estimates of this nature in Australia. We commonly prepare studies using a consistent method, which are used by policy makers and have been published in peer-reviewed literature. There are unfortunately limited data available on the type of delirium, and there are gaps as identified in the discussion and throughout the manuscript. However, we have removed “for the entire population” from the sentence to be clear that there are some gaps (Page 19, lines 338-366).

Reviewer: 2

Reviewer Name: Wolfgang Hasemann

Institution and Country: University Hospital Basel, Switzerland Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below. The authors have conducted the first study to estimate the economic impact of delirium in the Australian population using cost of illness methodology. The study provides novel insights in economics of delirium, uses a sophisticated

methodological approach, provides a fundus of enriched data and it is recommended to be published with minor revision.

The main text consists of 5000 words including references and tables. An appendix of 25 pages add tables and explanations to different sections of the article. The structure of the manuscript is consistent and well structured. The language is scientific and clear. The methodology section needs the addition of data collection, data analysis and ethical considerations.

Feedback to the sections in detail:

Title page – keywords: Keywords are either not Mesh terms nor are they very specific. Please revise

Response: The keywords are based on the list of keywords suggested by BMJ Open when submitting a manuscript. These keywords have been maintained.

Abstract:

P2.L12/13 The study is described as a “cost-of-illness study”. This term will not appear in the main text or in the appendix. Instead, cost-of-illness methodology is used. Please be consistent with the expression.

Response: The manuscript now consistently uses cost of illness study throughout, rather than cost of illness methodology.

P2. L55/56 “cognitive decline associated with delirium and dementia” comes unexpectedly. The expression dementia is mentioned for the first time in the abstract. It should be integrated as well into methods and results section.

Response: Thank you. Dementia has been integrated into the methods and results as suggested (Page 2, lines 6-7, 13-14).

Introduction

P4. L 7/8 There is a mismatch between the expression “often” (see “Delirium is a common, serious, and often-fatal medical condition”) and the mortality rates (hazard ratio 1.77) provided in table 1.5. Please adjust wording.

Response: Thank you. We have revised “often” to “sometimes” (Page 4, line 43).

P4. L9/10 Ref [1]. Please refer to a defining society or classification system.

Response: We have included additional words on the definition and diagnosis method (Page 4, lines 47-53, page 5, line 73-74).

P4. L16/17 Inouye (Ref [2]) doesn't use the expression “impaired cognition”. Please add corresponding reference.

Response: Inouye refers to disturbed cognition, although the sentence has been revised to reflect the DSM-5 definition (Page 4, lines 47-53).

P4. L24/25 “nursing time per patient” is not mentioned in Ref [2-4]. Please add corresponding reference.

Response: The reference to increased nursing time has been removed.

P5. L38/39 Please provide a reference

Response: The intention of these sentences was to describe the types of costs that may occur and the costs that have been included in the present analysis. We have moved these sentences to the start of the method section to make this clearer (Page 5, lines 83-90).

Methodology

P6 L5/6 “cost-of-illness methodology”

Response: The reference to cost of illness methodology has been removed here.

Please provide a reference P6. L 25/26 Please provide an example for “This approach is combined with both bottom-up and top-down approaches to estimate...”

Response: A reference has been provided, along with a sentence providing an example (Page 6, lines 97-100).

P7. L46/47 “attributable fraction approach” Please provide a reference to this method P9. L26/27 “friction cost method” Please provide a reference to this method P9. L57/58 “DALYs” Please provide a reference to this method P10. L3-7 “YLDs” “YLLs” Please provide a reference to this method

Response: Thank you. Additional references have been provided for these methods and terms.

P10 L31/32 Abbreviation first mentioned: AIHW

Response: Thank you. The abbreviation has been removed.

The following sections are missing: (1) data collection (2) data analysis (statistician? Software?) (3) Ethical considerations.

Response: A new section of data analysis and ethical considerations has been included at the end of the methods section (Page 14, lines 268-271).

Results:

P11. L 20/21 Please provide percentages of the population

Response: the percentage has been added, and we have also included the prevalence table from our supplementary file in the main document (Page 14, lines 276-282).

P12 Table 1: Please provide the numbers and percentages

Response: the percentage has been added.

Appendix:

P33 Table 1.2 Would it be possible to provide the percentages to the corresponding age group in the population?

Response: the percentage has been added. As noted, this table is now available in the main document (Page 14, lines 276-282).

P44 L22/23 Please "opportunity cost method" provide a reference to this method

Response: this section has been revised to make it more clear that we have assumed that the opportunity cost of a carer's time is the time they would otherwise spend in the labour force (Page 12, lines 222-224).

Reviewer: 3

Reviewer Name: Virginia Mumford

Institution and Country: Macquarie University Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for asking me to review this cost of illness study on delirium in Australia. This is a timely study and I have a few comments for review.

Page 4, para 1 – it might be more helpful to use the DSM 5 definition of delirium – the authors state that delirium occurs within the setting of a medical condition but some forms of delirium occur due to other factors – such as drug use. The definitions used by the authors could be confused with other forms of cognitive impairment, and does not include the element of inattention that forms a critical component of diagnostic testing.

Page 4 L55 – the authors should clarify that the studies indicate that delirium is the most common complication for the over 65s and also these studies were done in the Sweden not Australia

Page 5 L65 The authors should include the fact that there are validated tools for diagnosing delirium

Response: Thank you. Clarifications have been added in the introduction to address these three comments. We have included the DSM 5 definition and we also to clarify that there are tools to diagnose delirium (e.g. the Confusion Assessment Method) (Page 4, lines 46-53, and Page 5, lines 73-74). We have also revised the text about common complications, so that it is clear the study was completed in elderly hospitalized patients in Sweden (Page 4, lines 61-63).

Page 8 L141 It might also be helpful to add the delirium research awards from Dementia Australia.

Response: Thank you for this suggestion. In drafting the manuscript we had explored the availability of research grants offered by Dementia Australia. The latest available annual report showed that there were \$1 million in research grants for dementia related programs, some of which included diagnosis and prevention (i.e. likely related to delirium). However, we did not include these grants as it may double count the costs of dementia which have been attributed to delirium in our paper.

Page 15 L270 the authors should qualify that the figures for delirium are their estimates

Response: This clarification has been included (Page 20, line 359).

VERSION 2 – REVIEW

REVIEWER	wolfram weinrebe HFR Fribourg, Switzerland
REVIEW RETURNED	02-May-2019

GENERAL COMMENTS	The authors worked on a major revision of the paper. Only the discussion was kept in the original form which is acceptable if we regard the changes that have been added to the paper. 5 out of 6 questions/remarks were completed and explained. The only thing that leaves is the typology of delirium - here are no remarks or changings. That might be due to lack of information given in the documation systems used for analyzis. To my opinion, the results are clearer and the paper has been been finalized in a adapted strucure and content. The main message could not be changed and there rest same lacks but the results are ok. Publication is recommended.
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REVIEWER	Wolfgang Hasemann University Hospital Basel, Switzerland
REVIEW RETURNED	21-May-2019

GENERAL COMMENTS	Dear authors, Thank you for your thorough revision. All my comments have been addressed. There is nothing to add. Recommendation: ready for publication
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REVIEWER	Virginia Mumford Australian Institute of Health Innovation, Macquarie University, NSW, Australia
REVIEW RETURNED	05-May-2019

GENERAL COMMENTS	<p>Thank you for asking me to review the amended manuscript. There are a few outstanding issues that need to be addressed, especially related to clearly stating that the results are based on estimated numbers.</p> <p>P2 in the abstract the team need to clarify that the >132,000 cases of delirium is an estimate.</p> <p>P5 L91 this paragraph should be merged with the points in the previous paragraph,</p> <p>P7, Therefore, “we estimate” there were approximately 105,182 cases</p> <p>P8 L153 - is this an "episode" of delirium?</p> <p>P9 L159 In the summary for Ref 26 it states that 5.5% had delirium on discharge – and it is not clear where the 43% figure comes from - please clarify in the text.</p> <p>P14 L268 I assume this should be mortality not morality – in addition the discount rate of 3% seems low – is there a reason for choosing this figure?</p> <p>P16 L313 please state the year</p> <p>P22 L396 please state the year for the costs figures stated</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Thank you for asking me to review the amended manuscript.

There are a few outstanding issues that need to be addressed, especially related to clearly stating that the results are based on estimated numbers.

P2 in the abstract the team need to clarify that the >132,000 cases of delirium is an estimate.
Response: Thank you, we have taken greater care to ensure that the estimates are reflected as such. For example, we have also included “estimated” in table and figure titles to ensure this is clearer. Pages 14-17, lines 283-349.

P5 L91 this paragraph should be merged with the points in the previous paragraph.

Response: Thank you, we agree. These paragraphs have been merged. Page 5, lines 75-81.

P7, Therefore, “we estimate” there were approximately 105,182 cases.

Response: Revised as above. Page 14, line 271.

P8 L153 - is this an "episode" of delirium?

Response: Yes, we have added this clarification that it is at least one episode of delirium. Other studies have shown that aged care residents can go on to have multiple occurrences although this was not reported in the Boorsma et al data so we were unable to estimate exactly how many cases may occur. Page 15, Line 282.

P9 L159 In the summary for Ref 26 it states that 5.5% had delirium on discharge – and it is not clear where the 43% figure comes from - please clarify in the text.

Response: Thank you. Clarification has been added, noting that 5.5% of patients had delirium at discharge, although only 12.7% had delirium during their stay – 43% was derived as 5.5%/12.7%. Page 8, line 146-147.

P14 L268 I assume this should be mortality not morality – in addition the discount rate of 3% seems low – is there a reason for choosing this figure?

Response: Thank you. A reference has been added to support the use of this discount rate. The discount rate is also consistent with previous burden of disease analyses that suggested using a 3% discount rate (e.g. the Australian Burden of Disease study in 1999 and 2003). However, we recognise that more recent studies use alternate discount rates, including a 0% discount rate. Consequently, we have tested the one way effect of using alternate discount rates in the sensitivity analysis with an upper and lower bound. Page 12, line 236.

P16 L313 please state the year.

Response: The year has been stated. Page 17, line 294.

P22 L396 please state the year for the costs figures stated.

Response: Thank you. We have now included the year and the conversion rate for the estimate. Page 22, lines 395-396.