

Author's response to reviews

Title: Association between pain, neuropsychiatric symptoms, and physical function in dementia: a systematic review and meta-analysis

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Author's response to reviews: see over



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Subject Submission: revised original manuscript

Dear Dr. Mangiameli,

We have pleasure in submitting the revised manuscript entitled **Association between pain, neuropsychiatric symptoms, and physical function in dementia: a systematic review and meta-analysis (MS: 1365157972150652)** for possible publication in BMC Geriatrics.

Thank you for the valuable feedback, we have revised the manuscript accordingly. We believe these comments have significantly improved the manuscript.

The description of the point-by-point changes made are listed below.

If any additional information is required for the review process, please do not hesitate to contact me.

We look forward to hearing from you in due course.

Yours sincerely, also on behalf of my co-authors

A handwritten signature in black ink, appearing to read 'Annelore van Dalen-Kok', written over a faint dotted line.

Annelore van Dalen-Kok



Association between pain, neuropsychiatric symptoms and physical function in dementia: systematic review and meta-analyses

Reviewer's report 1

The revised manuscript by van Dalen-Kok and colleagues detail an interesting topic in the recent literature on dementia; the association between pain, neuropsychiatric symptoms and physical function, in demented subjects. The authors carried out a systematic review and meta-analysis, using a comprehensive methodology (search strategy, using a methodological quality assessment of evaluated studies, and calculating self-calculated ORs for studies). The manuscript is well written, with up-to-date reference. A clear flow diagram of the studies, as well as detailed tables and forest plots for the associations are also included in the manuscript. Lastly, the results and discussion sections (the latter includes a strengths and limitation paragraph) are soundly.

- a. Thank you for your positive comments.

Reviewer's report 2

Comments

1. The question posed by the authors is well defined; however, while adequate attention has been paid to the evaluation of the association between pain and NPS and Physical function, the description of the tools and methods used for pain detection (as proposed in the Background) seems to be less structured. I suggest the authors to improve it..

- a. We have added information in the methods section and results section as follows:

"Furthermore, we recorded data on the use of rating scales to measure pain, NPS and physical function, as well as the method of detection. For example, if pain was measured with a rating scale for observational behaviours indicating pain and who performed the observation, i.e. a research nurse, a professional or patient's proxy."
(row 157-160)

"Additional file 2 provides a complete overview of the methods used." (row 257)

2. The methods are appropriate and well described; some points should be better specified (see revisions).

- a. We agree with the reviewer. See the point by point revisions suggested in the 'Minor revisions' section below.

3. The data sound well, but there are some terms used in this article (i.e. article/study), that cause contextual misunderstanding.

- a. We agree with the reviewer that using the words 'article' and 'study' interchangeably is confusing. Throughout the entire manuscript we changed it to the word 'article'.

4. The figures appear to be genuine, without evidence of manipulation. Data are described objectively.

- a. Thank you.

5. The relevant standards for reporting and data deposition are satisfied.

- a. Thank you.

6. The discussion and conclusions are adequately supported by the data, but the importance of pain assessment tools validated for the population under study should be further stressed. For example, row 406 "Therefore, the results of the present review cannot fully support the hypothesis of a better reflection of the relationship between pain and NPS when validated rating scales are used by professionals ", but the importance of detection of pain in patients with moderate / severe dementia has not been sufficiently stressed. Pain detection is important because it could be the cause of other disorders (as your study wanted to prove), but primarily because it is a disturbing symptom for the patient and as such should be recognized, measured and treated.

- a. We agree with the reviewer and added a sentence in the discussion section-clinical implications:

"However, regardless of co-occurrence, we want to stress the importance of pain detection in patients with dementia because pain can be the cause of other disorders, such as NPS. Pain and it's consequences have an impact on the quality of life and therefore should be recognized, measured and treated." (row 499-503)

7. The limitations of the work are clearly stated; a further important limitation would be not to have considered Delirium as a related issue, potentially interfering with the variables under study (pain, NPS and physical function). The prevalence of delirium in patients with moderate and severe dementia is high, and the causal relationship between pain and delirium in these patients is well known. Furthermore delirium is a syndrome that includes both symptoms, NPS and alterations of the physical function. In your review I found no trace of delirium: why did you exclude it from your analysis? If you considered it, can you explain in which terms?

- a. We added this limitation in the discussion section, as follows:

"Another possible limitation is that we did not include delirium as a separate search term in our search strategy. However, as delirium is a syndrome with specific neuropsychiatric symptoms, we looked at the clinical features of a delirium by including these symptoms, such as hallucinations and delusions, in our search strategy." (row 467-471)

8. In the text it is not specified if the authors must cite any published or unpublished work upon which they are writing for.

- a. We added this sentence in the methods section:

"Only published data was included."(row 142)

9. The title and abstract convey with what I found in the text.

- a. Thank you.

10. The writing seems acceptable, but my language skills do not allow me to express an appropriate judgment.

- a. Thank you; the entire manuscript has been corrected by a native English speaker.

Major Compulsory Revisions

None

Minor Essential Revisions

Some minor revisions should be made to clarify the text:

1. In which range of time did you make the selection of the articles (it does not seem to be specified in the text)? Why are there no studies selected before the year 2002? Are there no studies, or is the quality of these studies not so high to be included in your review?

- a. We agree with the reviewer that this is not clarified in the methods section. There was no specific range of time in our search strategy. There were no studies before the year 2002 that met our inclusion criteria.

We added: "No time range or language restrictions were used." (row 147), to the methods section.

2. The cut-offs for the high quality studies are specified, but not those for moderate and low quality of the studies. Would you mind doing it? (rows 154-160).

- a. We added: "Cross-sectional studies that scored 0-4 points were considered to be of 'low quality', scores of 5-9 to be of 'moderate quality', and scores of ≥ 10 points were considered to be of high quality. For longitudinal studies, scores of 0-5 points were considered to be of 'low quality', scores of 6-11 to be of 'moderate quality', and scores of ≥ 12 points were considered to be of 'high quality'. (rows 167-173)

3. In "Scoring items" (rows 162-177) you selected the items used for the evaluation of the quality of the studies. Could you please enter more clearly how many articles and which articles have been used and what are the scores given for both types of studies?

- a. We've added a sentence in the methods section-Quality assessment: "See Additional file 3 for a more detailed overview of the awarded points and scores to the articles."(row 172-173)

4. In Additional file 2 you cite 19 articles, but in the text you mention only 15 articles (rows 239-245). Could you please clarify the mismatch?

- a. This section ('Measurement of Pain') has been revised and edited (row 246-257)

5. In the table 2 it can be deduced that in 3 out of 22 articles the rating scales are not used to measure pain. It would be useful to specify the data and to comment it in the text (row 245).

- a. This has been done. See also point 4a.

6. In Measurement of NPS (rows 236-245) you should, first of all, emphasize those studies in which the rating scales for NPS are not used and which are these studies; then you should indicate if in some studies more instruments to measure NPS were used simultaneously and which they are.

- a. This section has been edited (row 261-274).

7. Table 2 lists 11 articles, while studies that describe the physical function are only 10 (row 264). Using interchangeably the terms 'articles' or 'studies' may create misunderstandings (see also rows 197, 328, and others). Could you please specify which are the studies and which are the articles in the Methods, as well as in the Abstract.

- a. We revised the word "studies" into "articles" throughout the entire manuscript. See also point 3a of the Comments section above.

8. In the Results section, where you describe associations, would you mind specifying in how many articles you do not have correlation coefficients, ORs or SOORs?

- a. We agree with the reviewer that this is unclear. To clarify this we added: *“Furthermore, we excluded studies that did not report correlation coefficients, odds ratio’s (OR) or when the studies did not provide sufficient information to calculate the OR ourselves”* in the methods section ‘study selection’ (rows 145-147)

9. Add “(see Figure 2)” in the row 292.

- a. We have added *“(see Figure 2)”* in row 307

10. Add “(see Figure 3)” in the row 309.

- a. We have added *“(see Figure 3)”* in row 325
- b.

11. Add “(see Figure 4)” in the row 340.

- a. We have added *“(see Figure 4)”* in row 356

12. Table 6 lists 11 articles, while in the text you only cite 10 studies (see row 328): would you please clarify like at point 7 above?

- a. This has been edited, see also point seven and rows 343-357 in the manuscript.

Discretionary Revision

1. Why did you not include patients with Parkinson’s disease? (see Methods, row 139).

- a. Our diagnosis of interest was dementia as a primary diagnosis. In persons with Parkinson’s disease, dementia is often the secondary diagnosis. The same goes for Huntington’s disease, AIDS dementia complex and Creutzfeldt-Jakob syndrome.

2. The comparison between text and tables would be easier if you could insert a column in the tables referring to the numerical reference citations.

- a. We agree with the reviewer. We have added the numerical reference citations in superscript in the tables.

3. It would be useful to specify further what you mean by “intentionally selected population” and “unintentional selected population” (rows 215-216).

- a. We have clarified the text, as follows:

“Five studies described the use of selection criteria, mostly on NPS, and in eight other studies there might have been an indirect (unintentional) selection on pain, NPS or functioning For instance, an indirect selection on pain by including patients with pressure ulcers [8].(row 229-231)

4. You ought to specify the reference of the studies that used rating scales “which are validate to assess behaviour in patients with dementia” (see row 253).

- a. We have edited this section (row 261-274).

5. Could you specify how many studies used the MDS-ADL and which they are (see row 268)?

a. We changed the sentence into:

“Five articles used the MDS-ADL scale for measuring patient’s physical function (Table 2). This was also the most frequently used measurement[3,8,32,39-41].”(row 280-281)

6. Please could you specify the range of prevalence for specific NPS, ie depression (row 284), agitation (row 296), and other NPS?

a. The range of prevalence does not include all studies reporting on prevalence rates of depression, agitation, etc, as this was not the scope of our review.

Reviewer’s report 3

[Methods of the review are described and appear to be sound. However, the checklists used should be introduced in more detail as they cannot be considered standard instruments. This also applies to the criteria mentioned in the “scoring items” section. It remains unclear if all criteria are listed in this section or if it only contains examples. How are the procedures described in the “quality assessment” section and the “Scoring Items” section connected? The authors may consider amalgamating these two sections to improve clarity]

1. Please introduce the checklists used in more detail as they cannot be considered standard instruments. This also applies to the criteria mentioned in the “scoring items” section. It remains unclear if all criteria are listed in this section or if it only contains examples. How are the procedures described in the “quality assessment” section and the “Scoring Items” section connected? The authors may consider amalgamating these two sections to improve clarity.

a. To improve clarity we added an additional file with the checklists. See additional file 3.

[How are the search terms used connected to the stated aim of the study? Why was “depression” selected as a search term but not agitation, for example? Why has only the abbreviation “BPSD” been used as an umbrella for all behaviours under consideration? It appears that this choice of search terms may be a cause of bias. The same applies for the terms used to search for “physical functioning”.

The authors may want to clarify why the terms presented were chosen and elaborate on the risk of bias with their selection, especially with regards to the studies that were identified and selected.]

2. Please clarify why the terms presented were chosen for the literature search and elaborate on the risk of bias with this selection, especially with regards to the studies that were identified and selected.

a. Additional file 1 displays the search terms used in this systematic review. To be more specific we added a sentence to the strengths and limitation section: *“Also, we explicitly searched for publications about pain and not for terms like ‘distress’ or ‘discomfort’.* However, we believe that this approach provides the best reflection of the complex relation between pain, NPS and physical function.”(row 459-462)

Discretionary Revisions

[This article presents work on an important geriatric issue and furthers the insight into the association between pain and other geriatric symptoms. The aim of the manuscript is clearly stated, while a research question per se has been omitted. This is, however, acceptable as the purpose of the article becomes clear. However, it would be helpful if the authors in the background section could elaborate in a little more detail on why attention should be paid to measurement instruments, as this then is referred to in the aim of the review and in the discussion section.]

1. Please elaborate in a little more detail on why attention should be paid to measurement instruments, as this then is referred to in the aim of the review and in the discussion section.

a. We added a sentence to the background section:

“Nevertheless, there are validated measurement instruments available to detect pain in patients with dementia, such as the PACSLAC, DOLOPLUS2, and MOBID-2, based on observations [59,60]. Adequate use of these measurement instruments is of utmost importance in the management of pain.” (row 100-103)

[The study data and results are reported adequately. The discussion appears comprehensive and sound. The authors may want to elaborate further on the term “distress”, though, that is introduced in the discussion section as opposed to pain. The difference between the two concepts may not be meaningful to all readers and may even be an issue for controversy.]

2. Please elaborate further on the term distress and the difference to pain.

a. We agree with the reviewer that the introduction of the term ‘distress’ in the discussion could be confusing. Distress is an important topic in the care for persons with dementia; it might be an important cause of challenging behavior. However, distress as a possible causal mechanism deserves more attention and elaboration than it receives in this review. As this is beyond the scope of this review, we have decided to remove the elaboration on the term distress in the discussion section.