Author’s response to reviews

Title: Medication adherence influencing factors – an (updated) overview of systematic reviews

Authors:

Alina Gast (alinagast@online.de)
Tim Mathes (tim.mathes@uni-wh.de)

Version: 1 Date: 07 Feb 2019

Author’s response to reviews:

Thank you very much for the opportunity to revise our manuscript. We responded all comments. All changes of the content in the manuscript were made using track changes.

Reviewer #1:

Abstract/Synthesis of results:

Page: 3 Line: 57, please did we really need these sentences, as stated: "There was no funding for this overview. The overview was not registered", however the registration component of this sentence may appear here, but the funding idea I questioned it.

Response: We deleted these sentences in the abstract.

In addition, look at the bottom of Synthesis of results section, Page: 6 Line: 38 to 41 and make the changes, as already stated above, as the idea is not appropriately placed.

Response: We removed the sentence and placed it directly under the method section (page 3, Line: 87-89).

Background:

Page: 4, Lines: 7 to 26, adding more background information will enhance understanding of the topic; currently this section content is too brief.

Response: Thank you for this suggestion. We added further background information (page 3).

Risk of Bias Assessment of individual studies and across studies:
Page: 6, Line: 7 to 9, please revisit this sentence: "The risk of bias assessment of these SRs was therefore performed by another reviewer to avoid as biased assessment. ", and convey appropriate meaning.

Response: Thank you for the hint. We rephrased the sentence to ensure appropriate meaning (page 6, line 179-181).

Characteristics of included systematic reviews:

Page: 8 Line: 29 to 30, was it not appropriate to show to readers of this review how you arrived at the figure 0.5%: The Corrected Covered Area (CCA)

Response: We added the formula for calculating the CCA in the “Synthesis and results” section (page 7, line 200-205) and now provide all relevant variables for calculation in the “Characteristics of included systematic reviews” section (page 8, line 232-235).

Final Comments:

closely appropriate systematic approach to the documentation of this OoSRs. An improved version is needed, after updating current version based on comments raised.

Reviewer #2:

1. The title is confusing.

What does the authors mean by the overview (update). Why not a systematic review?

Response: This study is a systematic review of systematic reviews, which is called Overview (of systematic reviews). We believe that this is meanwhile an established terminology (see for example the Cochrane handbook, or McKenzie and Brennane BMC SR 2017). For clarification we added “systematic review” in the title. It is an updated version of an overview published by our research team in 2014 (https://www.ncbi.nlm.nih.gov/pubmed/?term=Mathes+T%2C+Jaschinski+T%2C+Pieper+D.+Adherence+influencing+factors+--+a+systematic+review+of+systematic+reviews), as described in the methods section (Information sources) on page 3, line 92-93. Therefore, we called it “update”, The word update is in brackets because we applied a somewhat different approach (more focused) in the first version.

Also consider to include the wording medication adherence.
Response: Thank you for this suggestion. We revised the title accordingly.

3. Please specify the age limits instead of adults and children in the manuscript inclusion and exclusion criteria.

Response: Thank you for this idea. We specified the age limits. Adults are defined as patients ≥ 16 years old (page 4, line 108).

2. The authors should include other language literature. Though mentioned as a limitation, in this day and age there are many tools available to translate the manuscripts from other languages

Response: There were no financial resources for a professional language translation. Research has shown that translation with GoogleTranslate or other automatic translation tools cannot be expected to be error free (https://www.ncbi.nlm.nih.gov/pubmed/24199894). Especially a reliable translation from non-Germanic or Spanish languages (e.g. Sino-Tibetan or Afro-Asian) into English is problematic.

Reviewer #3:

Abstract:

Line 30, delete "might"

Response: We replaced “might” with “can” (now line 31).

Line 34, what does (06/2018) mean? Is that the beginning or end of the study?

Response: We performed a systematic electronical literature research in June 2018. We replaced (06/2018) with the search date (June the 13th 2018) to ensure appropriate meaning (now line 35-36).

Why only Medline and Embase? Why not other databases?

Response: Research in library science (https://www.sciencedirect.com/science/article/pii/S0895435606001272) has shown that searching only Medline and EMBASE is sufficient for an overview (systematic search for systematic reviews). Also according to the Risk of Bias in Systematic Reviews Tool (https://www.bristol.ac.uk/media-library/sites/social-community-medicine/robis/robindocument.pdf) a literature search in Medline and EMBASE provides the minimum range of databases to be appropriate for an overview.
Line 57 is not necessary
Response: We deleted the line.

Background:
The significance and rationale of the study is not adequately explained?
Response: We added further information in the Background section (page 3).

Method:
"The search was performed on June the 13th 2018". Was the search conducted only in one day?
Response: We prepared electronic search filters for Medline and EMBASE (see supplement I). We run these searches in Medline and EMBASE on June the 13th 2018, which resulted in 4849 hits after duplet removal. We run/performed the search only on this day. We tried to clarify the text (page 4, line 102-103).

Line 92, Adult patients with physical chronic diseases? What does physical mean? Which chronic diseases?
Response: We included all chronic diseases which can affect physical health. As described on page li 93 f., we excluded acute conditions and patients with mental illnesses. We revised the text for clarification (page 4, line 108-111).

What if the primary studies composed of adult and children mixed?
Response: We only included adult and children mixed studies if these groups were reported separately or min. 80 % of the study population were adults (max. 20 % children). We added this information in our eligibility criteria (page 4, line 109-110).

When did we say a patient adhered according to this manuscript? 90%, 95% intake? Adherence should be clearly defined in the primary systematic reviews and follow nearly similar pattern? Even what was the measurement of adherence (self-report, table count, biomarker). As this parameter widely vary among studies it will also case significant heterogeneity among studies making difficult to combine the findings. How this heterogeneity issue was handled in the primary systematic review and this SR of SRs?
Response: We fully agree that this is an important issue. We considered the validity of the adherence measure in the risk of bias assessment. Unfortunately, as you expected the adherence definition in the primary studies varied widely and we could not find a way for sufficient harmonization, i.e. a harmonization that allows pooling. We did not calculate effect sizes but only performed a structured narrative synthesis. Therefore, from a statistical point of view,
different adherence measures are not that important because in the worst case heterogeneity implies that an existing association was not found (but not a spurious finding). We considered this heterogeneity in our assessment of inconsistency/heterogeneity. Thus, if we found an association this is a quite robust association in the sense that it seems to exist independently of the heterogeneity that might be caused by different adherence measures.

We clarified the text and added this as limitation (page 12-13, line 403-406).

Results:

It'd better to present the result in graph or table for easy understanding

Response: We present the results of the synthesis in table 3. We used arrows and signs for easy understanding. To the best of our knowledge there are no methods to present the results of an overview in a graphical way.

Discussions:

How and why ethnic minority negatively affects adherence needs discussion. What does ethnic minority mean? It's clear that ethnic minority in one geographical area could be ethnic majority in other geographic area.

Response: Thank you for this suggestion. We discussed the results on ethnic minorities in more depth (Discussion section page 13, line 411-417). In addition we added your comment, that an ethnic minority in one geographical area could be an ethnic majority in another geographical area.

The effects of many of adherence influencing factor is uncertain in this study. And this is systematic review of systematic reviews. Could we, therefore, concluded that "adherence cannot be predicted based on the factors stated in the manuscript"? Or else can we recommend better study with novel methodology? If so, what method?

Response: We fully agree with you that our findings are probably caused by the quality of evidence. We extended our discussion of the flaws of the existing SRs and future research (page 14, line 449-453).
Declarations

Remove the track changes.

Response: Thank you for the hint. We removed the track changes.