15-Feb-2021
BMJ-2020-063284 entitled "Accuracy of the Hospital Anxiety and Depression Scale Depression Subscale (HADS-D) to Screen for Major Depression: Systematic Review and Individual Participant Data Meta-analysis"

Dear Dr. Thombs,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Regards,
Timothy Feeney MD MS MPH
Research Editor
The BMJ
tfeeeney@bmj.com

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=b9490ac2ec744078b8bd9196948e5a0a

**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair); Tim Cole (statistician); Wim Weber; John Fletcher; Joseph Ross; Tiago Villanueva; Nazrul Islam, Timothy Feeney

Decision: Put points

Detailed comments from the meeting:
First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

Thank you for submitting your paper. We are impressed with the scope of the study, and feel that the results will be informative. We do have some comments and suggestions for improved clarity.

* The forest plots are currently unsorted. Please consider sorting by the sum of sensitivity and specificity to make them much easier to read.
* Would the authors consider overall accuracy estimates for different cut-off as an easier to digest summary measure (otherwise we need to juggle between sensitivity and specificity).
* The editors are concerned conclusions might be stronger than the evidence supports since there isn’t that much difference between 7 and 8 as cutoffs. In fact another message might be that the original paper proposing cut offs for HADS-D did a fairly good job even with such little data.
*Please see the statistical review by Dr. Nevitt for additional comments.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
This is an outstanding piece of scholarship and a valuable contribution to the literature. The authors very thoroughly and systematically assessed the measurement properties of the Hospital Anxiety and Depression Scale depression subscale as a screening measure for Major Depressive Disorder.
Uncharacteristically, for me, I have absolutely no concerns. The manuscript is very well written. It is fascinating that the optimal cut-point, >=7, is lower than that used by almost anyone using the HADS-D.

Additional Questions:
<em>The BMJ</em> uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from <em>The BMJ</em>, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our <a href="https://www.bmj.com/about-bmj/resources-reviewers" target="_blank">peer review terms and conditions</a>.
Comment:
This is an important synthesis of studies examining the diagnostic operating characteristics of the depression subscale of the Hospital Anxiety and Depression Scale (HADS). The HADS is among the top 3 or 4 most widely-used depression scales, and this state-of-the-art meta-analysis is useful to both
clinicians and researchers. Strengths include the large number of studies available for the meta-analysis, the use of individual participant data, the comparison of findings using different reference standards, and detailed sensitivity analyses. Comments are minor.

Comments

1. Introduction, p. 12, it is stated that the HADS “is recommended for assessing the severity of depressive symptoms by the UK National Institute for Health and Care Excellence.” I believe that the HADS is not the sole measure recommended by NICE but one of several depression measures. If that is the case, the sentence should be phrase as “one of several validated measures recommended for assessing…”

2. P. 18, Methods, and p. 21: Heterogeneity was evaluated using two statistics -- $\tau^2$ and R. Many are more familiar with I2, for which cutpoints of 25%, 50% and 75% represent thresholds for low, moderate, and high heterogeneity, respectively. What are the thresholds for $\tau^2$ and R to represent different levels of heterogeneity? For example, the Results indicate that heterogeneity was “moderate” by R and $\tau^2$ and refer readers to Supplementary Table 3. However, most readers will not know how to interpret the absolute values for R and $\tau^2$ in terms of what represents low, moderate, and high heterogeneity. The authors should add a footnote to Supplementary Table E to indicate what thresholds are for interpreting R and $\tau^2$, at least for “moderate” heterogeneity.

3. P. 18, it is stated that interactions were added to the meta-analysis for “all QUADAS-2 items with at least 100 major depression cases among participants categorized as having “low” risk of bias and among participants with “high” or “unclear” risk of bias.” This sentence is rather cryptic and should be better explained. It is probably too terse and adding a few more words or splitting the sentence in two might be clearer.

4. On p. 20, it states there “158 unique participant samples. Of these, 92 (58%) contributed datasets … Among 14 eligible studies published before 2000, only 1 (7%) contributed a dataset; among studies published between 2000 to 2009, 31 of 57 (54%) contributed datasets; and among those from 2010 to 2018, 60 of 88 (68%) contributed datasets.” The total of 14 + 57 + 88 equals 159 (not 158). Please reconcile.

5. There are several other competing depression measures, of which the PHQ-9 (on which the authors have done a similar meta-analysis) and the Beck Depression Inventory along with the HADS are among the more commonly used. The authors might acknowledge this in the Discussion and state whether these are largely comparable measures from a screening standpoint and, if so, whether head-to-head studies are needed.

Additional Questions:
<em><strong>The BMJ</strong></em> uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.<em><strong></strong></em>

If this manuscript is rejected from <em>The BMJ</em>, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our <a href="https://www.bmj.com/about-bmj/resources-reviewers" target="_blank">peer review terms and conditions</a>. 
Please confirm that you understand and consent to the above terms and conditions:

I consent to the publication of this review

Please enter your name: Kurt Kroenke, MD

Job Title: Professor of Medicine

Institution: Indiana University School of Medicine, USA

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <a href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests" target="_new">(please see BMJ policy)</a> please declare them here: I have no completing interests with respect to this article

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: No

Reviewer: 3
Comments:
I have conducted a statistical review of the manuscript "Accuracy of the Hospital Anxiety and Depression Scale Depression Subscale (HADS-D) to Screen for Major Depression: Systematic Review and Individual Participant Data Meta-analysis."

The authors present an individual participant data bivariate meta-analysis and meta-regression examining the diagnostic test accuracy of different cut-offs of the HADS-D as a screening tool for major depressive disorder.

Firstly, the authors and wider collaborative team should be congratulated for bringing together over 25,000 participants data from over 100 studies to perform such an in-depth analysis with promising clinical implications if the lower cut-off is adopted within screening of major depressive disorder.

Overall, the statistical approach seems mostly appropriate and results are well presented. I have made a few comments on the methods and presentation of results, as well as some minor wording comments.

Comments on methods and presentation of results:
1) It wasn’t clear to me throughout the manuscript whether the MINI as a reference standard was classified as a fully structured interview or not. For example, the eligibility criteria define only 'semi-structured or fully structured interview' as eligible reference standards and the MINI seems to be listed within the QUADAS-2 descriptions of the reference standards as a fully structured interview (Supplementary Methods B). However, within analysis, the MINI is treated separately to semi structured and fully structured interviews.

From my own knowledge of the MINI, I agree that it doesn't really fit into either category of semi-structured or fully structured interview, but it is a validated measure. I’d suggest that the MINI should be treated as a separate reference standard category throughout the manuscript for consistency, rather than being included as a 'fully structured interview' for some elements of the work.

2) Statistical analysis, page 18: I am not following how interactions for risk of bias (i.e. QUADAS-2 domains for each study) have been handled in the participant level meta-regression models. Risk of bias domains apply on the study level (i.e. it is the study that has a risk of bias rather than the participants), therefore introducing participant level QUADAS-2 domain variables don't represent a participant like their age, sex etc. does, but rather is a measure of the study they happen to have been recruited into.

I suggest that it would be more appropriate to account for risk of bias in these models by sensitivity analyses; such as a sensitivity analysis excluding studies at high risk of bias or a sensitivity analysis restricting only to studies at low risk of bias.

3) Meta-regression results (Supplementary Table C and G): Please give more meaningful names to the left-hand model coefficient columns so it is clear to a reader what each row corresponds to.

I also suggest that further explanation of some of the information in these tables may be needed, such as any reference categories used within the regression. How should d0 and d1 be interpreted (e.g. model intercepts)?

4) Supplementary Table F (subgroup results): If I understand correctly for Supplementary Tables F, the 'difference' is based on all participants and a subset of all participants?

If so, how where the sensitivity and specificity with 95% CIs calculated taking account of the overlap in the two groups being compared? Or should the subgroup comparison here be, participants currently diagnosed or receiving treatment for a mental health problem compared to participants not currently diagnosed or receiving treatment for a mental health problem?

Also a few wording related comments:
5) Data extraction, page 15: "Participant-level data included age, sex, cancer diagnosis, patient care setting, HADS-D scores, and major depression status (case or non-case)."

Minor point, I assume this list of data refers to both data requested as IPD and also data extracted from study reports where no IPD were available?
6) Statistical analyses, page 18: "...we generated nomograms for assumed major depression prevalence of 5-25%.”

Minor point, were percentages were chosen for illustrative purposes, i.e. as in the introduction, it is stated that "major depressive disorder (MDD) is present in 10–20% of patients with acute or chronic medical conditions”, i.e. 10 to 20% +/- 5%? It may help to clarify this choice of prevalence percentages or provided a reference.

7) Figure 1: I suggest it would be helpful to also add into the cell which describes the 66 studies without primary data (IPD) provided, how many of the studies reported data which could be extracted and included in sensitivity analyses.

8) Supplementary Table B: Related to the previous comment, "Could” study have been added as a published dataset? I suggest it would be better to state 'Was published dataset included in sensitivity analyses?” or similar for clarity of exactly which data are included in analyses and which data are not.

9) How was the cut-off of 60 years determined for the age categories presented in Table 2? (I note that age was analyses as a continuous variable in meta-regression).

10) Results, page 21: "As shown in Supplementary Tables D1-D3, estimates did not change when these results were included.”

This isn’t quite accurate as there are some minor changes to the numbers. Perhaps rephrase to 'estimates were the same to 1 decimal place' or 'conclusions did not change'?

11) Discussion, paragraph 1: "HADS-D sensitivity was 1% to 11% higher when it was compared to semi-structured interviews...”

1% to 11% here refers to across the cut-offs examined?

12) Discussion paragraph 4: “The finding that HADS-D accuracy estimates were the best when compared to semi-structured reference standard” Please quantify what is meant by 'best' here. E.g. the highest estimates? The most precise? The estimates with the least heterogeneity?

13) Conclusion, last sentence: "Well-designed trials are needed to determine whether screening with the HADS-D would improve mental health outcomes and minimize harm and resource use.” Does this sentence refer to screening with the HADS-D in general, or screening specifically with a cut-off of ≥7?

Additional Questions:
<em>The BMJ</em> uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.<em>/em></strong>
For more information, please see our <a href="https://www.bmj.com/about-bmj/resources-reviewers" target="_blank">peer review terms and conditions</a>.

Please confirm that you understand and consent to the above terms and conditions.:
I consent to the publication of this review

Please enter your name: Sarah Nevitt

Job Title: Research Associate

Institution: University of Liverpool

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <a href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests" target="_new">(please see BMJ policy)</a> please declare them here: I have no competing interests

<em>BMJ are working with <a href="https://orcid.org/" target="_blank">ORCID</a> to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.</em>

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.</em>

Would you like to be accredited by <a href="https://orcid.org/" target="_blank">ORCID</a> for this review?: Yes