

<b>Article details: 2020-0283</b>	
Title	The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis
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<b>Reviewer 1</b>	Thomaz Bastiaanssen
Institution	
General comments (author response in bold)	<p>The authors present a timely meta-analysis of the potential positive effect of microbiome-targeting therapies in depression. These types of meta-analyses are important and healthy for the field. The manuscript is also presented as a review of the field. In that regard, a lot of discussion is missing. when more discussion on the different ways in which microbiome studies and their analysis are conducted and how this affects interpretation is included, this manuscript will be a valuable addition to the field.</p> <p><b>Thank you, the objective of this manuscript has been clarified (page 3).</b></p> <p>-It would be useful to give some more background on (potential) mechanisms that are targeted in a microbiome intervention study (eg vagus nerve, immune system, SCFAs, neuroactive molecules etc)</p> <p><b>Thank you, the objective of this manuscript has been clarified (page 3).</b></p> <p>- Please make it clear when referring to animal research or human research when citing articles.</p> <p><b>Thank you, this has been clarified (page 4).</b></p> <p>- In the section “Interpretation”, the authors discuss the issue of power in microbiome studies. This remains an open question in the field. Could the authors expand on this and give (estimates of) recommendations in this regard? It would greatly benefit the impact and utility of the paper.</p> <p><b>Thank you, this has been clarified (page 10).</b></p> <p>The citation software used seems to have given error messages throughout the manuscript.</p> <p><b>Thank you, this has been adjusted throughout.</b></p>
<b>Reviewer 2</b>	Alessia D'Elia
Institution	Psychiatry and Behavioural Neurosciences, McMaster University
General comments (author response in bold)	<p>This manuscript reports the findings of a systematic review of gut microbiota-altering interventions on depression. The inclusion of the PRISMA reporting checklist was excellent to ensure transparency of reporting the review. Your conclusions based on the presented findings are appropriate and generate excellent directions for future research. Please see my comments below related to improving the manuscript.</p> <p><b>Thank you.</b></p> <p>Placement of references inconsistent in the manuscript (reference at times before and after the period). Some further revision of grammar and structure would help with the flow of the manuscript.</p> <p><b>Thank you, reference placement has been made consistent, and grammar/structure has been improved throughout.</b></p>

You may consider revising your title to read “A systematic review and meta-analysis of the effects of gut microbiota-altering interventions on depressive symptoms.” This study considers clinical and community populations of individuals without depression, has no restrictions on study population, and uses depression outcomes, therefore it would perhaps be appropriate to amend your title to more accurately capture your research objectives.

**Thank you, the title has been modified to be consistent with CMAJ Open Style.**

Page 8, Line 10. Was a protocol published for this review? If yes, include the link to this publication.

**The protocol was not published. PROSPERO registration number is provided beneath the abstract.**

Page 8, Line 44. Consider including whether any calibration phases/training were conducted to train reviewers on the protocol and systematic review objectives.

**Thank you, this has been clarified (page 4)**

Page 8, Line 34. Were qualitative and observational studies excluded from this study systematically? Perhaps state this more explicitly if applicable.

**Thank you, inclusion and exclusion criteria has been clarified (page 4).**

Page 8, Line 44. Were trials that assessed a combination treatment (i.e., gut microbiota-altering interventions and psychotherapy/exercise/etc) included? Was this a specific exclusion?

**Thank you, inclusion and exclusion criteria has been clarified in table 1.**

Page 9, Line 12. Data Extraction and Quality Assessment: Were articles screened using a specific platform? I.e., Covidence or DistillerSR online platforms, or Microsoft Excel.

Page 13, Line 51-53. Consider changing this sentence to read: “All three funnel plots in show a lack of studies finding benefits of interventions with small standard error, suggesting the presence of publication bias,” for clarity.

**Thank you, this change has been made (page 9).**

Page 13, Line 25. Consider making a statement about the implications of the level of bias observed.

**Thank you, this has been added (page 12).**

Page 15, Line 42-46. You mention that a strength of the review is the inclusion of all validated tools measuring depression. In the methods you mention that: “Outcomes evaluated with single item Likert scales or visual analogue scales were excluded.” I would amend this statement slightly to more accurately reflect the inclusion of tools measuring depression.

**Thank you, this has been clarified (page 11).**

Figure 2. Consider providing a more descriptive figure caption for Figure 2.

**Thank you, a more descriptive figure caption has been added to figure 2.**