Author's response to reviews

Title: Association Between BDNF Levels and Suicidal Behaviour: A Systematic Review Protocol

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Author's response to reviews: see over
Dear Drs. Moher, Shekelle, and Stewart,

Thank you for your feedback on our manuscript, *Association Between BDNF Levels and Suicidal Behaviour: A Systematic Review Protocol*. We have revised our manuscript with your questions and comments in mind, and we have responded to them below (in bold).

Reviewer’s comments:

This protocol is generally well written and addresses an important problem. I am not familiar with this specific area of research, so I don’t know if there are many or few studies likely to meet the inclusion criteria, and the authors may wish to consider my comments in light of their knowledge about the field. Overall, the protocol should try to anticipate the decisions the authors will need to make in conducting their study.

1) The inclusion criteria potentially include a very wide range of studies (perhaps the first protocol I’ve seen to include post-mortem as well as community-based samples). It’s not clear from this manuscript how the authors plan to deal with (i) different study designs in (ii) different populations (iii) making different comparisons. I assume the whole range of potentially eligible studies would not be combined in a single meta-analysis, for example. What are the comparisons of interest, relevant subgroups, etc. and how will the authors deal with clinical heterogeneity arising from these different sources? They might solve these problems by narrowing the inclusion criteria to a more similar group of studies or by explaining how the review will deal with a very diverse group of studies.

These comments were helpful in identifying a need for clarification in our methods. We agree with the reviewer that a single meta-analysis will not be performed for the reasons clearly outlined by the reviewer. Our goal is to look at the whole spectrum of suicidal behaviour, including completed suicide, so we chose to include both postmortem and clinical studies in our review. We will separate the studies based on the type of suicidal behaviour (completed suicide, attempted suicide, and suicidal ideation) and, if appropriate, we will conduct separate meta-analyses.

i) Study design: We will combine the results from studies with similar study designs. For example, case control studies will be combined separately from cohort studies.

ii) Population: We will combine the results from studies investigating a specific suicidal behaviour. For example, studies investigated BDNF level in completed suicide will be combined in a meta-analysis if appropriate.

iii) Comparisons: The comparison of interest in this review is the level of BDNF in individuals who have engaged in suicidal behaviour compared to individuals who have not engaged in suicidal behaviour. We will combine the results from studies with similar comparisons. For example, studies comparing serum BDNF levels in individuals with and without a suicide attempt will be combined in a meta-analysis.

Subgroups will be based on the type of suicidal behaviour as described above.
We will attempt to minimize clinical heterogeneity by including studies with similar designs and suicidal behaviour subgroups. If heterogeneity remains, we will discuss the implications on the interpretation of the results. We aim to have an inclusive review of BDNF and suicidal behaviour, and our ultimate goal is to define this association for each type of suicidal behaviour. While it would be easier to narrow our inclusion criteria to a more similar group of studies, we believe this would restrict the knowledge generated by this review to a limited group of individuals.

In the section entitled “Statistical analyses and heterogeneity,” we have expanded our explanation of how we intend to deal with this diverse group of studies (lines 168-177).

2) How will the authors deal with different measures of suicidal behaviours and studies that include more than one measure? What about different time points?

Thank you for raising these points. For studies that include multiple measures of suicidal behaviour, the most common validated measure will be used. For studies that report different time points for suicidal behaviour, we will consider only the most recent event. We have now addressed these questions in the section entitled “Data Extraction” (lines 142-144).

3) Finally, the search strategy is very short but appears to include sensible terms. I wonder if this has been validated for studies of suicide or if there are validated filers for the area?

While the search strategy does appear short, it was devised with the help of an experienced health sciences librarian, and includes an appropriate set of search terms. We were careful to include as many search terms as possible to encompass the topic of suicidal behaviour and BDNF. Upon implementing our search strategy, we retrieve a total of 557 articles.

We look forward to hearing from you.

Best regards,

Rebecca Eisen and Dr. Zainab Samaan