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,

We would like to thank the editors and the reviewer for the helpful feedback on our manuscript, *Association Between BDNF Levels and Suicidal Behaviour: A Systematic Review Protocol*. We have further revised our manuscript with the reviewer’s comments in mind, and we have responded to them below (in bold).

Reviewer’s comments:

My earlier comments identified major limitations in the protocol, which have not been addressed adequately (http://www.systematicreviewsjournal.com/imedia/1123410759161793_comment.pdf).

Here are the original 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 community/clinical studies in our review. We will separate the studies based on the following characteristics: the study design, the type of suicidal behaviour (completed suicide, attempted suicide, and suicidal ideation), and the site of BDNF measurement. For all studies to be included in each subgroup, we will provide a qualitative summary of the studies and their findings, and when appropriate, we will conduct separate meta-analyses, providing an adequate number of studies is available for each subgroup.

Below we provide more specific answers to each comment raised by the reviewer:

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.
For each study design, we will only combine studies that examined the same type of suicidal behaviour and BDNF measurement. For example, case control studies that measured brain BDNF levels in completed suicide will be combined in a meta-analysis if appropriate.

ii) Population: We will combine the results from studies investigating a specific suicidal behaviour. For example, studies investigating brain BDNF level in completed suicide (postmortem) will be combined in a meta-analysis if appropriate. Case control studies of clinical samples (e.g., individuals with depression and a history of suicide attempts compared to a control group without suicidal behaviour) will be combined in a qualitative summary of such studies, and, if appropriate, in a meta-analysis.

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 if appropriate.

We have added additional detail to the section entitled “Statistical analyses and heterogeneity” in order to better explain our analysis plan and the anticipated diversity of studies to be included in this review (lines 193-237). We have now clearly presented our intention to group the studies based on specific shared characteristics, and to perform meta-analyses on those groups if appropriate. We will attempt to minimize clinical heterogeneity by including studies with similar design, suicidal behaviour, and BDNF measurements. Heterogeneity will be assessed using the $I^2$ statistic, and an $I^2$ value below 50% will be considered low heterogeneity. A p value below 0.10 will be considered significant heterogeneity. We predict that a main source of heterogeneity will be diversity in the sample populations. For example, comparisons of suicidal depressed groups with non-suicidal controls are commonly seen in case-control studies of clinical samples, whereas studies of suicidal behaviour in a community sample are seen in cohort studies. If significant heterogeneity remains, we will discuss the implications on the interpretation of the results.

Our primary aim is 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.

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?
For studies that include multiple measures of suicidal behaviour, we will record all measures reported. This will allow us to combine studies with the most commonly used measures in meta-analysis. For studies that report different time points for suicidal behaviour, we will consider all time points and combine similar time points from the different studies if appropriate. We have addressed these questions in the section entitled “Data Extraction” (lines 154-166):

For studies that include more than one measure of suicidal behaviour, each measure will be recorded. This will allow for the combination of studies with the same measures in a meta-analysis. For example, some studies have used the suicide item in Hamilton Depression Rating Scale (HDRS), while others have used the Beck Scale for Suicidal Ideation (BSS) [25, 26]. We will record all measures reported so that we can combine, for instance, all studies that used the BSS. We expect most studies to report suicidal behaviour as a dichotomous measure (e.g., history of suicide attempt or no history of suicide attempt). However, if studies used different measurement scales to indicate severity of suicidal behaviour, then we will use a dichotomized outcome based on the presence of suicidal behaviour, regardless of severity.

For studies that report multiple time points for suicidal behaviour (e.g., suicide attempt within the last month, vs. the past three months, vs. lifetime), all time points will be recorded. This will allow for the combination of similar time frames when possible.

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 filters for the area?

While the search strategy does appear short, it was devised with the help of an experienced health sciences librarian, and includes a set of search terms suitable for the subject of this review. We were careful to include as many search terms as possible to encompass the topic of suicidal behaviour and BDNF. The search terms chosen are ones that are common in the literature. Upon implementing our search strategy, we retrieve a total of 557 articles. We have added additional details regarding in the section labeled “Search strategy” (lines 123-134):

The search strategy (presented in Table 1) will use relevant keywords and their associated medical subject headings (MeSH). A number of different search terms related to suicidal behaviour that are common in the literature will be used in order to encompass this broad topic, including “suicide”, “attempted suicide,” “self-injurious behaviour”, “self harm*,” “automutilation,” “self inflict*,” and “suicidal ideation.” These terms will be combined with the terms “brain-derived neurotrophic factor” or “BDNF”. The search will include titles, abstracts, and keyword fields. The reference lists from the included articles will be scanned manually to identify additional studies. Only primary published studies will be included; reviews, abstracts, and commentaries will be excluded. No language restrictions will be applied. An experienced health sciences librarian (LB) was
consulted and assisted in the search strategy. A search alert will be set up to ensure the retrieval of relevant studies published after the initial search.

Additionally, changes to the data extraction plans (i.e., extracting the most common measure of suicidal behavior) are at odds with changes to the plans for statistical analysis (i.e., separate meta-analyses will be performed for different measures of suicidal behavior). The protocol does not describe fundamental issues about plans for selecting and synthesizing studies. Major revisions (i.e., MUCH more detail about every aspect) are still required to make this a transparent and replicable plan for a systematic review.

We have revised our data extraction plan to address that apparent contradiction. We will extract all measures of suicidal behaviour reported, and we will combine those studies that used the same measures in a meta-analysis. We have added much more detail throughout this protocol in order to ensure the transparency and replicability of our systematic review, particularly to the section entitled “Statistical analyses and heterogeneity” (lines 194-238), discussed above.

In addition to the changes discussed above, we have added to the following sections:

Under “Inclusion and Exclusion Criteria,” we have explained that, “Included studies will have investigated the association between levels of BDNF and suicidal behaviour by comparing BDNF levels between groups with and without suicidal behaviour” (lines 112-114) We have also specified that, “No demographic limitations will be applied apart from age, and no special populations will be excluded (e.g., incarcerated individuals, pregnant women, etc.)” (lines 116-117).

We have added the following under “Assessment of Quality” (lines 185-190):

The Grading of Recommendations, Assessment, and Evaluation (GRADE) framework will be used to report the quality of evidence and strength of recommendations [29]. This framework provides a systematic approach for considering and reporting risk of bias, imprecision, inconsistency, indirectness of study results, and publication bias. A summary of findings table will be presented, to allow for assessment of confidence in the estimates.

We look forward to hearing from you.

Best regards,

Rebecca Eisen and Dr. Zainab Samaan