Author's response to reviews

Title: The contribution of major depression to the global burden of ischaemic heart disease: a comparative risk assessment

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Author's response to reviews: see over
Response to reviewers

The authors thank the reviewers for their valid comments and feedback. Responses have been written and several revisions have been made to the manuscript.

Reviewer: Kenneth Freedland

Minor essential revisions

1. The Methods section of the Abstract states that the review’s strict inclusion criteria “were designed to provide evidence of a causal relationship.” This is a stronger statement about causality than is expressed throughout the remainder of the manuscript, and it goes beyond the data. Although the included studies were prospective, and although population attributable fractions were determined, this sort of analysis cannot prove causality. It would be better to stick to noncausal terminology, e.g., “independent risk factor”.

Response: The strength of the word causality is noted and amendments have been made throughout the manuscript accordingly.

Refer to lines 37, 77, 79, 269, 310-314,

2. In the main body of the manuscript, the Methods section says nothing about how IHD-free status was determined at baseline in the included studies. It would be better to describe the participants as being free of clinical manifestations of IHD at baseline. The authors acknowledge on p. 11 that signs of IHD can be difficult to detect and subclinical in nature. This can make it difficult to ensure that all subjects were IHD-free at baseline, and the problem is not limited to mild, subclinical IHD. Many individuals have advanced coronary disease and silent myocardial ischemia without realizing it and without seeking medical attention for it. Some even have silent myocardial infarctions without realizing it, or at least without seeking medical attention for it. The only way to form a completely IHD-free cohort is to enrol children. The authors should briefly acknowledge the inherent difficulty of studying incident IHD in adult cohorts.

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3. On a related point, the IHD endpoints were defined as well as one could hope, given the nature of the available studies. Also, by differentiating between fatal and nonfatal events, the authors have shown that depression is a stronger predictor of mortality than of other CV events. However, the downside of modelling IHD events is that coronary artery disease can reach clinically significant status without triggering a clinically recognized IHD event or intervention. There may be no obvious way to take undiagnosed cases into account, but did the constituent studies at least count cases in which clinically significant CAD had been diagnosed in the absence of an IHD event or intervention?

Response: The suggested description of IHD-free status has been altered in the ‘Box’ of inclusion and exclusion criteria.

It is true that it was difficult to take undiagnosed cases of IHD into account given the nature of this study. Unfortunately there were no studies identified that detected silent IHD – all used a
cardiovascular event such as MI, angioplasty, coronary artery bypass or death as the endpoint. Under-estimation of asymptomatic IHD prevalence is a limitation of the studies included in our pooled analysis of the association between IHD and depression. We added a specific statement that “silent” IHD was not included in the IHD definition of either the GBD or the IHD-depression studies reviewed. Because the asymptomatic IHD cases would be classified as “no IHD” in these studies, the effect would be to dilute the magnitude of the association. The end result is that we may have conservatively under-estimated the association between IHD and depression. We therefore added the following statement to the Limitations section:

“The GBD 2010 Study did not include “silent” IHD in its case definition because for the purposes of the study only symptomatic (i.e., disabling) diseases were measured. None of the IHD-depression studies included from our review included “silent” IHD. Because some cases of “silent” IHD were possibly classified in the “no IHD” group in these studies, the implication is that these studies under-estimated the association between IHD and depression, making our estimates overly conservative.”

Refer to lines 108-109, 365-376

4. It is unfortunate that all of the studies that were based on self-report depression measures relied on the CES-D. It has one of the worst track records of any depression questionnaire in terms of prognostic value in established CHD. If data on the BDI had been available, there might have been less of a difference between the diagnostic and questionnaire studies. A brief note about this could be added to the Discussion.

Response: The authors agree that measures of depression such as the CES-D are not optimal. We would prefer to see studies utilising diagnostic and/or well-validated instruments. Unfortunately this is not currently available in the literature and should ideally be an area of attention in future research. We have explored the differences in relative risk associated with diagnostic methods versus other instruments, noting that appears that instruments not truly representative of a diagnosis may underestimate risk. An additional sentence has been added to the discussion to highlight the inadequacies in measurement of depression.

Refer lines 365-367

5. Incomplete sentence at the top of p. 8.

Response: The sentence at the top of page 8 has been corrected

Refer line 222-223

Reviewer: Peter de Jonge

Major compulsory revisions

1. The authors have based their effect sizes on 12 US and 1 NL study and generalise these effects to the global burden. I do not think this is wise. Perhaps the authors should restrict themselves to US or Western culture.
2. In the discussion they argue that the effects of depression are mainly biological and therefore easily generalised across the globe. In my opinion, this is a very bold statement and quite in contrast to most of what we know. It appears to me that the few studies that have done some kind of mediational analysis have found that physical exercise and smoking are in the most promising mediators for this association. And even if so, then it still does not mean that all cultures are interchangeable.

Response: The authors note the gaps in the data and the implications this has in terms of generalisability, however, the decision to estimate attributable burden for regions where there was no data has been a standard position taken by the Global Burden of Disease Study 2010 [1, 2]. Whilst contentious, the view is taken that to not provide estimates for regions with missing data is to infer that burden does not exist. The implications of this are considered unacceptable and estimates have been produced whilst simultaneously calling for action in the research community to fill data gaps [3]. The limitations of this approach have been widely discussed and are generally accepted.

It is important to note that variations in regional attributable burden estimates are developed using three sources of data - regional prevalence of depression, regional prevalence of ischaemic heart disease, and the relative risk of depressed (versus non-depressed) subjects developing ischaemic heart disease. Regional prevalence estimates for the 21 world regions have been estimated in a separate component of GBD 2010 and have been published in the peer-reviewed literature (insert refs). The concerns about generalisability across regions arise from the relative risk component only. Having said this, the authors acknowledge that perhaps the limitations have not been discussed at sufficient length and we have amended the discussion accordingly.

Refer lines 310-314, 322-338

3. The authors should address the possibility that MD and CVD may have bidirectional effects or are both representing an underlying process instead of focusing only on the unidirectional effects of depression on CVD. It could also be that anxiety (e.g. social phobia) which often precedes depression is the real factor that 'produces' the effect. In my opinion, the authors give a bit too simplified picture of the association.

Response: The authors acknowledge this very valid point. We had briefly alluded to the potential confounding effects of anxiety but have extended this point in the discussion.

Refer lines 339-355

4. Related to this, they refer to the association as 'effect' and 'causal' but I do have a problem with this. There are no intervention trials in which depression was treated in order to reduce IHD risk. The only ones that did, in patients with established IHD, were negative in terms of reducing CV death or recurrence. The status of the association does not appear causal to me. They refer to a recent debate in this journal on this topic but unfortunately included on one side of the argument (positive) and failed to include the other (negative).
Response: The authors also consider this a valid point. Further extended reference to the poor evidence that depression treatment in fact lowers risk of IHD has been made in the manuscript.

Refer lines 315-321

5. the authors have found an indication for possible publication bias. Could they correct for this?

Response: Unfortunately without accessing unpublished studies we are unaware of a satisfactory method of correcting any publication bias.

