Reviewer's report

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

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Reviewer: Peter de Jonge

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I found this paper of considerable interest. The authors addressed the question whether depression may have a contribution to the global burden of disease via the incidence of ischaemic heart disease. They did so by a systematic review of the literature and a quantification of the summarized effects. I do have a series of comments:

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.

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.

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 reduced 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).

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

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests