Reviewer's report

Title: Sex dependent risk factors for mortality after myocardial infarction: individual patient data meta-analysis

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Reviewer: Jess Fiedorowicz

Reviewer's report:

Van Loo and colleagues present the results of meta-analysis (patient level) of interaction between risk factors following myocardial infarction. The manuscript is exceptionally well written, the analyses rigorous, and the results provide novel information not found in the existing literature while confirming in a convincing way previously reported interactions.

Major Compulsory Revisions:
None

Minor Essential Revisions:
1) The method discuss categorization of depression into three classes based on z-scores (with highest value being top quartile), yet the results discuss 40% having an increased depression score based on standard cutoffs. Please clarify. I personally appreciate the additional presentation of the categorical cutoff measure, but it would help to have a sense of what thresholds were used. It would also be helpful to report in the methods what depression measures were collected in each study (could also consider table for this).

2) Table 1 refers to “increased depression score” yet this is a baseline variable. “Increased” implies the value changed over time. Please reword (e.g., “elevated”) in a manner that doesn’t imply that a prospective change over time was observed. Please also clarify whether smoking refers to current smoking.

3) The protective effect of the lowest quartile of depression is fascinating and suggestive that these symptoms are relevant even outside the pathological range. Perhaps this can be at least briefly discussed. It may argue for not simply focusing on depression as a categorical disease in conveying risk. It is interesting to think that even within the normal range lower levels of depression might be protective.

4) Please clarify the following from the discussion: “For instance, why is depression more strongly related to all-cause mortality in men than in women? A study in one of the datasets included in MINDMAPS suggested that men with depression are more likely to have a poor LVEF than women with depression.[37] Thus, depression seems to reflect more severe heart disease in men but not in women,
which could explain why depressed men are more at risk for all-cause mortality than depressed women.

This example illustrates that the interpretation of interactions should be done in the context of possible confounders.” In Table 2, I was under the impression that the interactions were tested controlling for other variables (such as LVEF and Killip class), thus the sex differences observed seem unlikely to be fully explained by severity. If I'm misunderstood, please clarify in the manuscript accordingly.

Discretionary Revisions:

1) Antidepressant use appeared harmful and I wonder if this was due to collinearity with depression (and lack of a protective effect). Could the authors at least report the percentage of those in the highest quartile of depression treated with antidepressants? If low, this is reassuring. If collinearity appears potentially problematic, please consider reporting a sensitivity analysis that either excludes antidepressants from the models or collapses it into the high depression group (perhaps as a categorical group by merging with increased depression score).

3) Highest quartile of depression is difficult to extrapolate to other research studies and clinic. Can the authors comment on what this approximates with one or two of the more commonly used depression scales used.

Other Comment:

1) Figure 1 is a very nice addition to the manuscript.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.