Reviewer’s report

Title: The impact of depression and anxiety treatment on biological aging and metabolic stress: study protocol of the MOod Treatment with Antidepressants or Running (MOTAR) study

Version: 1 Date: 27 Oct 2019

Reviewer: Martino Belvederi Murri

Reviewer's report:

- Re. "feasible in clinical care and conducted in line with current guideline standards" and "Both interventions were conducted using evidence-based clinical guidelines"; should add a citation to the specific guidelines you refer to. Also, contact with a psychiatrist and a "running therapist" may not be entirely equivalent from an outcome point of view. I am not saying that either is superior, but the study, similarly to other similar studies, cannot answer the question whether contact with staff is partly responsible for clinical improvement (akin to non-specific psychotherapeutic effects). I suggest to add a point in the limitations section re. this issue.

- "We thank the reviewer for the suggestion to indeed refer to this PRPP design which is indeed in line with our design." Since you had not clearly consulted indications re. this study design in the first place, I think it is highly inappropriate to refer to it now, after conducting the trial (Post-hoc justification). "in line" is too generic in my opinion. Please be more specific as to: 1) the exact process of enquiry for patient preference and 2) the type of partial randomization protocol you had planned to adhere while planning the study. Point 2 especially in the part related to data analyses.

- I agree on the high rates of overlap between anxiety/depression but the diagnosis should be at least considered as a confounder. The limitations should report on this point.

- There is evidence on the efficacy of exercise, true, but studies are still highly needed. Especially if they employ original designs, use different protocols and recruit different diagnoses. So I don't think these motivations are/were sufficient to discard efficacy as the primary outcome. What if you find a benefit on telomere length, but NOT on efficacy? Would this be sufficient to recommend this intervention in clinical practice? Clearly not. In my opinion, the clinical relevance of telomere length (or HPA axis, or HRV or other biological mechanisms) is at present suggestive (potential mediating mechanisms), while actual clinical improvement is still crucial. And here is the main problem of seeking publication of the protocol late: it can't be changed now. I think this point should also be part of the limitations.

- Please add more detail on the study intervention. E.g. what approach to fatigue, symptoms during the intervention, adverse events, presence of a physician, etc. I am quite surprised that even with older patients potentially participating, there was no thorough cardiologic screening.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?  
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No

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