Author’s response to reviews

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

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Author’s response to reviews:

Concerns: revision of manuscript (BPSY-D-19-00468): 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, by Lever-van Milligen et al.

Date: September 24th, 2019

Dear Mrs., Mr.,

We are pleased to be given the opportunity to send in a revised version of our manuscript entitled “The impact of depression and anxiety treatment on biological aging and metabolic stress: study protocol of the MOod Treatment with Antidepressants or Running (MOTAR) intervention” (BPSY-D-19-00468).
We are glad that the reviewers found the findings of our study relevant. We have addressed all points raised by the reviewers below and have revised the manuscript accordingly. We found the comments to be most helpful and believe that they have led to an improved manuscript.

We would appreciate your consideration of this manuscript for publication in BMC Psychiatry. Should you have any questions, please feel free to contact the corresponding author.

Yours sincerely,
B.A. Lever-van Milligen, Msc

Response to reviewer:

#1 Reviewer reports:
Martino Belvederi Murri (Reviewer 1): The study protocol described the motar study, comparing antidepressants and running for patients with anxiety or depressive disorders. Several mechanisms of efficacy are being measured (biological and psychological). Another important point of originality of this study is to take in account patient preference re. allocation to treatment. Given the wide variability in patients' preferences and beliefs re. efficacy, I think this adds very useful information, although this choice brings along some problems as well. First, the study has already been carried out since several years (2012- 2019). The publication of the study protocol before starting recruitment might have been more useful (it might have allowed some adjustments).

Author’s reply:
We would like to thank the reviewer for his positive comments on our paper. With regard to the timing of publication of the study protocol, we think the most important criterion is that the protocol is published before data-analysis starts, which is the case in our study. We agree with the reviewer that critically reviewing a study design is of utmost value. However, this study design has been critically reviewed by multiple researchers and clinicians in earlier stages, i.e. when applying for funding (the Dutch Scientific Organization), by submitting the study protocol to the Medical Ethical Committee and by registering this trial in the Trial register. In our opinion changes to a design should not be made easily following this stage.

Second, another important limitation, in my opinion, is the likely imbalance between the two groups in terms of contacts with psychiatrists. If I understood correctly, the antidepressant group will see a psychiatrist at least 4 times during 16 weeks while the running therapy group sees the (trained and clinic-affiliated) running therapist 3 times per week during 16 weeks. So, the patients in the running group will receive more intensive contact time with staff compared to the antidepressant group. To emphasize that both interventions are based on clinical guidelines, the following sentences was added to the method section page 13: ‘Both interventions were conducted using evidence-based clinical guidelines’.

The following sentence was added to the method section page 13: ‘Both interventions were conducted using evidence-based clinical guidelines’.
Third: authors stated they adopted a "pragmatic" approach for the study design. However, various approaches have been used to encompass patient preference into clinical research while attempting at reducing bias. It would be important to compare and discuss differences/implications with other designs. E.g. "partially randomized patient preference" design (PRPP). Here, participants are interviewed re. their treatment preference before enrolment, then only those without a clear preference are randomized. Lambert et al Journal of Clinical Epidemiology Volume 53, Issue 2, February 2000, Pages 163-166). Another interesting example is the "Doubly Randomized Preference Trial" approach (Zoellner et al., Am J Psychiatry 176:4, April 2019). The adopted design, together with the inclusion of various psychiatric disorders, increases the risk of having findings that are difficult to interpret. There is a consistent risk that treatment groups will be unbalanced also in terms of diagnoses (anxiety vs. depressive disorders), as well as personality and other "hidden" unmeasured features. Also, it is unclear what is the proportion of the subsample of patients who will be (have been?) randomly allocated (e.g. 20-40% of the total or using a cutoff based on preference). Also, what is the rationale for this choice, and was it decided a priori?

Author’s reply:
Indeed, we decided a-priori to ask the patient if he/she is willing to be randomised, and if not willing, whether he/she wanted to be included and follow the treatment of their preference. The rationale for this choice was to increase recruitment efficiency and to be able to examine whether there are any differences in effect of therapy in the randomised and preference group. The latter would give us more information on the extent to which randomisation has resulted in selectivity of our sample.

We thank the reviewer for the suggestion to indeed refer to this PRPP design which is indeed in line with our design. We added in our method section the following words: ‘… a pragmatic study with a partially randomised patient preference design (PRPP)…’ with the reference of the article of Lambert et al. (2000). The advantage of this design is that following the patient preference is not seen as bias to randomisation, but it contains potentially important prognostic information and it increases the recruitment of the study.

Furthermore, the reviewer suggests that there are various psychiatric disorders included in this study. This true as we included anxiety disorders and depressive disorders irrespective of the specific diagnosis. We choose to do so because these disorders are highly comorbid (e.g. our NESDA project which recruited in the same setting yielded a comorbidity of 78% (Lamers et al. 2011)), and over time there is quite some instability between these disorders with many depressed patients developing anxiety (Verduijn et al. 2017) and vice versa (Scholten et al. 2016). Consequently, comorbidity is the rule not the exception, especially in specialised mental health care where recruitment of our study take place. In addition, the underlying pathophysiology of both disorders is largely comparable and both disorders are treated often with similar treatment regimen (antidepressants) and running therapy has shown to be effective in reducing both depressive as anxiety symptoms (Strawn et al., 2016, Cipriani et al., 2018, Mead et al. 2009, Carek et al. 2011). So we don’t think that it is inappropriate to focus on both depression and anxiety disorders, as separating these highly interlinked disorders will be difficult.

To make the rationale for including both anxiety and depressive disorders more clear, we now describe why we decided to include both depression and anxiety patients in our trial more clearly on page 9, where we extended the text with: ‘Depressive and anxiety disorders are highly comorbid (Lamers et al. 2011), also over time (Verduijn et al. 2017, Scholten et al. 2016), their underlying pathophysiology is largely comparable and both disorders are treated with similar treatments (Strawn et al., 2016, Cipriani et al., 2018, Mead et al. 2009, Carek et al. 2011)’.

Personality and many other clinical, lifestyle or somatic indicators will be measured at the assessment and can be considered in the analyses. We think we captured most important variables in this study that
may play a role in the effect of the treatment programs on biological aging. The reviewer suggests that there may be other “hidden” unmeasured features. Indeed it could be that there may partly be some selectivity in patients choosing for running therapy or antidepressants, but the randomisation part of our RCT will compare treatments that were randomly assigned. We believe it is very informative to see whether effects are differential or not depending on the randomised versus non-randomised assignment.

Fourth: why biological aging was chosen as the primary outcome instead of a clinically important one (e.g. remission?). In my opinion "pragmatic" trials are far more interesting for their clinical implications and translation potential, while the "real world" implications of telomere length are by far more unclear. The risk of mortality associated with telomere length, for instance, is significant but relatively weak (Mons et al., Am J Epidemiol. 2017 Jun 15;185(12):1317-1326.; Darrow et al., Psychosom Med. 2016 Sep;78(7):776-87). I suggest the authors pre-specify how they will derive "biological aging" from the two indices (telomere length and telomerase activity).

Author’s reply:

The reviewer wonders whether a clinically important outcome such as remission should be a better outcome for the study. We agree on the relevance of clinical outcomes. However, the clinical effects of both treatment interventions have been widely examined before and generally – rather comparable – efficacy has been indicated (Cipiriani et al., 2018, Schuch et al. 2016, Kwam et al, 2016). The meta-analysis of Kwam et al. (2016) for instance showed that there are 3 earlier studies (Blumenthal et al. 1999, 2007, 2012) that have directly compared antidepressant treatment with running therapy intervention and found no difference in clinical effect. Based on these studies, we assume that the clinical effects are not different. To verify previous findings we will test this in our study. However, the innovative approach in this study is to examine whether interventions have a differential effect on physiology. Therefore, biological aging is our primary aim. We have chosen for telomere length as our primary marker of biological aging. Telomere length have been shown to be effected by multiple physiological stress systems such as the immune-inflammatory system, the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS) (Revesz et al., 2014, Revesz et al., 2016). So, it is a cumulative biological aging marker that picks up various underlying pathophysiological changes. It has been associated with aging but also with the development of many somatic illnesses. Telomere length and telomerase activity have earlier been used as outcomes in studies examining the effects of various interventions (Puterman et al. 2010, Conklin et al. 2018, Le Noygen et al. 2019) and show significant, even at short-term, effects of lifestyle on the reverse of telomere length. However, the effects of running therapy and antidepressants on telomere length are still unclear. Furthermore, our study is the first that included two different interventions and compares their effects on biological aging in a psychiatric sample. We hypothesize that the effects of running therapy as compared to antidepressants will not differ on the clinical outcomes, but may be different at the biological aging level. To explain our choice of primary outcome, the following sentence was added to the method section (primary outcome, page 13): ‘TL has been shown to be correlated to the functioning of multiple physiological stress systems such as the immune-inflammatory system, the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS) (Revesz et al., 2014, Revesz et al., 2016) and therefore picks up potential improvement in various underlying mechanisms. In addition, TL has been shown to be predictive of various somatic health outcomes including mortality. TL has earlier been used in studies examining the effects of lifestyle interventions (Puterman et al., 2018, Conklin et al., 2018, Le Noygen et al., 2019) and has shown sensitive to change as, even at rather short term, interventions were linked to less shortening of telomere length. In addition to explore the underlying telomere system dynamics, we also will measure telomerase activity, as was done in Wolkowitz et al, 2012.’.
As the reviewer suggested, we now have specified how biological aging will be derived with the following sentence which was added to the method section (Primary outcome): ‘Less shortening of TL after treatment will be seen as reverse of biological aging’.

Minor issues
- It is unclear how patients who will undergo neurobiological assessments are selected. Also, in my opinion, the paragraph dedicated to MRI assessment is overlong relative to other parts (e.g. no description of HRV and several other indices), considering that only a subset of participants will be assessed. Also, please add few details on HPA axis measurements (how many per day? How many days?).

Author’s reply:
We thank the reviewer for noticing this omission. We now added the following sentence to the method section, paragraph ‘recruitment’: ‘All patients are asked to participate in the MRI substudy.’. We agree with the reviewer that paragraph about MRI assessment is overlong. As the reviewer suggested, the description of the neurological assessment was shortened by deleting the explanation of two MRI tasks (page 16), leaving the following paragraph in the manuscript: In a subsample of the patients and in the healthy controls a neuroimaging assessment will be taken using the 3T Philips Intera MR system. The 15-words test, a Dutch version of the Rey’s auditory verbal learning test [114] will be performed outside the scanner to assess verbal episodic memory. Anatomical T1-weighted and diffusion tensor imaging (DTI) scans will be obtained to assess grey and white matter structure. An emotional face matching paradigm [115] and N-back paradigm [116] will be employed to examine task-related brain activity. Finally, brain network connectivity will be examined during rest by acquiring resting state fMRI images.

As suggested we added details about the HPA axis measurement in the method section (secondary outcome). The following sentence was changed: ‘and six saliva samples were taken at one day covering morning awakening response (at awakening and at 30, 45 and 60 minutes later), afternoon (at 6 pm) and evening (at 10 pm) levels’.

- Authors should provide more details on the type of matching between study participants and healthy participants

Author’s reply:
We thank the reviewer for this suggestion. We added the following sentence to the recruitment section: ‘Patients and controls are matched on the basis of age, sex and educational level.’.

- Do participants receive any type of incentive? (economic, other)

Author’s reply:
Indeed, for each assessment the participant will receive a gift voucher of €50,- and for each MRI-assessment, the participant will receive a gift voucher of €25,-. The controls will receive a gift voucher of €50,-. We added this to the method section (consent and assessments).

- Eligibility: how is current physical activity recorded? Is past use of antidepressants or psychotropics recorded? This may be important for post-hoc analyses. Please add details on suicide exclusion (e.g. instrument used, criteria for ideation or attempt) and pregnancy
Author’s reply:
Current physical activity will be asked in the telephone screening by checking the eligibility criteria: ‘during last month, how many times per week did you exercise?’. Patients will be excluded when they exercise more than 1 time per week. This criterion is now better described in the ‘Eligibility section’ on page 11: exclusion criterion ‘number 3) regular exercising, more than once a week’.
Past use of psychotropic medication in prior weeks will indeed be asked for during the assessment at week 0, 16 and 52. The following sentence was added to the secondary outcomes (depressive and anxiety disorders) page 14: ‘Psychotropic medication use was assessed during the interview at baseline, 16 and 52 weeks by inspection of the participant’s medication containers. It contained lifetime history of use as well as use during the study and was classified using the World Health Organization Anatomic Therapeutic Chemical (ATC) classification (World Health Organization Centre for Drug Statistics Methodology, 2010).

Suicide exclusion was based on the impression of the clinician who informed the patient about the study. We added to the exclusion criterion of suicidal risk: ‘based on clinical view’.

Being pregnant is an exclusion criteria since pregnancy has a large of impact on physiological processes which likely bias the results. This was added to the Method section (Eligibility) as a 7th exclusion criterion.

- What are the contra-indications to running therapy? I argue a cardiologist visit/EKG may have been necessary for all participants, considering the inclusion of people aged up to 70 yo.

Author’s reply:
Contra-indications of participating in the running group are physical complaints such as heart problems or a severe disease. During the telephone screening the following question is asked: ‘Are you hindered for participating running therapy by eg. physical complaints or a severe disease?’ When physical problems or disease are present, the general practitioner will be contacted for possible contra-indications for taking part in the running therapy. This was shortly mentioned in exclusion-criterion number 6 (medical contra-indications to running therapy or antidepressants (e.g. serious heart problems) as confirmed by a physician). We specified in the manuscript that is concerns patient’s own physician.

- What is the size of running groups? Will it be outdoors or indoors?

Author’s reply:
The size of the running group is on average 5 or 6 patients and will be performed outdoors. When needed (e.g. under severe weather conditions) indoor running is also possible. In the description of running therapy it was described that running therapy will generally be performed outdoors. The next sentence was added to the method section (Running therapy): “The size of the running group is on average 5 or 6 patients.”.

Chad Rethorst (Reviewer 2): This manuscript details a study protocol aimed at examining the effect of two depression treatments (antidepressant medication and exercise) on markers of biological aging. While the study is likely to make a meaningful contribution to the field, more detailed descriptions of
some aspects of the study methodology are necessary.

1. The authors state that treatment assignment will be based on patient preference and patients "without strong preference" will be randomized. The authors should describe the process in which preference will be determined and how those without a "strong preference" will be identified.

Author’s reply:
We decided a priori to ask the patient is he/she is willing to be randomised. If a patient did not agree to randomisation, he/she was invited to participate in the treatment of their preference. The rationale for this choice was to increase recruitment success. In addition, it will allow us to examine whether there are differences in effect of therapy in the randomised and preference group and to examine in which extent a randomized group is or is not more selective. The first reviewer adequately suggested to refer to this better as the PRPP (partially randomised patients preference) design as has been introduced before. We added in the Method section (Study design, page 9) the following words: ‘… a pragmatic study with a partially randomised patient preference design (PRPP)…’ with the reference of the article of Lambert et al. (2000).

2. Please provide further detail on the running intervention. The running sessions will be led by a staff member. Will these sessions include multiple participants or will these session be conducted one-on-one with the staff member?

Author’s reply:
We thank the reviewer for his suggestion and added the following sentence to the Method section (Running therapy), page 13: ‘The size of the running group is on average 5 or 6 patients’.

3. The stated purpose of the study is to "examine and compare the impact of antidepressant medication and running therapy on biological aging..." However, the statistical analysis does not include plans to compare the two treatments, and the power calculations are based on detecting a within-group change in the markers of biological aging.
4. Are any analyses planned to examine the effect of treatment preference? For example, do people who prefer exercise as a treatment achieve similar or greater benefit compared to those who were randomized to exercise?

Author’s reply:
We agree with the reviewer’s opinion about missing details in the statistical section about comparing the treatment groups and changes in the groups. The following sentence of comparing the effects of the two treatment programs was added to the Method section (Statistical analyses): “The two intervention groups will be compared using mixed models or generalized estimating equations (GEE) to assess the longitudinal change of biological aging, physiological and metabolic stress and psychiatric symptoms. These models will also evaluate the differences in physiological and clinical effects of those who are willing and not willing to be randomised.”.

References


