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

Authors:

Bianca Lever (b.lever@ggzingeest.nl)
Josine Verhoeven (j.verhoeven@ggzingeest.nl)
Lianne Schmaal (lianne.schmaal@orygen.org.au)
Laura van Velzen (laura.velzen@orygen.org.au)
Dóra Révész (D.Revesz@uvt.nl)
Catherine Black (c.black@ggzingeest.nl)
Laura Han (l.han@ggzingeest.nl)
Melany Horsfall (m.horsfall@ggzingeest.nl)
Neeltje Batelaan (n.batelaan@ggzingeest.nl)
Anton van Balkom (t.vanbalkom@ggzingeest.nl)
Digna van Schaik (a.vanschaik@ggzingeest.nl)
Patricia van Oppen (p.vanoppen@ggzingeest.nl)
Brenda Penninx (b.penninx@vumc.nl)

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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: November 28th, 2019

Dear Mr. Byrne,

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 addressed all points raised by the reviewer and revised the manuscript accordingly. We believe the quality of the manuscript has improved and we would like to thank the reviewer for his comments.

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:

#1Reviewer reports:
Martino Belvederi Murri (Reviewer 1): - 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.

Author’s reply:
We thank the reviewer for carefully reading our response letter and for his additional comments on the revised paper. As suggested by the reviewer, we added a citation to the specific guidelines we referred to (page 13): Psychiatry treatment guidelines (Multidisciplinary guidelines depression and anxiety (in Dutch)) (https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_depressie_3e_revisie_2013.pdf).

We agree with the reviewer that we cannot answer the questions whether contact with staff is partly responsible for clinical improvement. We see the difference in the number of contacts as part of the different treatment programs and we realize that the number and types of contacts with clinicians is not similar between the two groups. In the Discussion (page 18) of our paper we now state that: ‘As the number and type of clinician contacts between groups are not similar, this could be underlying clinical improvement. However, the interventions in this trial were developed in line with current guideline standards and therefore are as much as possible reflective of regular clinical care treatments.’

"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.

Author’s reply:
For MOTAR the inquiry regarding patient preference was conducted as follows. We first checked respondents’ general eligibility criteria. If eligible, the design of MOTAR was introduced in which the emphasis was placed on the randomisation design. We explained that both interventions are effective, but that our study was set up to examine underlying mechanisms of both interventions. Persons who
were willing to be assigned to the intervention through randomisation were randomised using the SPSS random generator (SPSS, version 20.0). If persons were not willing to be randomized to interventions, they are allowed to receive the preferred intervention.

We see overlap between the PRPP design, which we now refer to only more distantly. We changed the design section on page 9 according to your suggestions:

‘A randomised controlled trial is the preferred method to compare two interventions, but also comes with limitations: quite some patients do not agree with random treatment assignment, and therefore, studies may result in selective inclusion of subjects which hampers the generalizability of results. Consequently, we decided to conduct a pragmatic study (resembling a partially randomised preference patients design (PRPP) [79]). First, patients without strong preference for treatment allocation are randomly allocated (1:1) to either antidepressant medication or running therapy. Subsequently, persons who were not willing to be randomised but are willing to participate in the study, were allocated to their preferred intervention.’

In the statistical analyses section of the manuscript it is written that the analyses of examining the effects of the intervention will be evaluating in the total sample as well as in those who are willing and who are not willing to be randomised. Comparing those groups (randomised vs. not randomised) will give insight whether following patients’ preferred intervention has a different effect on biological aging, psychiatric status and neurobiological abnormalities. We added the following sentence to the statistical analysis plan section (page 17):

‘These models will also compare physiological and clinical effects of those who are willing and not willing to be randomised to check the impact of a patients’ preferred or allocated intervention’.

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.

Author’s reply:
We agree with the reviewer that the type of disorder is something that deserves attention in the analyses of our study. On page 15 we added the following sentence: ‘The type and number of depressive and anxiety disorders will be compared across the intervention groups and, if necessary, considered as covariates in the main analyses.’

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.

Author’s reply:
First, we would like to notice that both antidepressants medication and running therapy have shown to be clinically effective in reducing depression and anxiety symptoms and are currently included in the depression and anxiety clinical guidelines.

We completely agree with the reviewer that examining and comparing efficacy of both interventions is
highly interesting and therefore we included diagnoses and symptom severity scores of depression and anxiety as our outcome measures. However, our primary outcome – as described in the original research application and in the IRB protocol and patient information folders is biological aging since our main research question was to examine whether both treatments are similarly effective in reducing or reversing biological aging. We believe it is unethical to subsequently change the ordering of primary outcomes. Also we still believe that understanding whether or not the processes through which different interventions work, and what their impact is beyond mental health outcomes, are highly relevant. In our case, we do not a-priori expect much difference in depression/anxiety outcomes by exercise versus medication interventions as earlier trials that directly compared these interventions have found both interventions to be quite similarly efficacious (Blumenthal et al. 2007,Netz et al., 2017). The novelty of this study is that we will be able to look at which (biological) mechanisms change due to different interventions and to what extent these are co-occurring with treatment response, thereby providing a stronger basis for personalised medicine.

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.

Author’s reply:  
During the screening phase and during the baseline assessment, so before formal inclusion/randomization to the study, potential physical and/or somatic problems and use of medication are administered. When serious somatic conditions are signalled, the person’s own physician will be contacted and consulted in order to discuss potential study participation. Furthermore, at the beginning of the running intervention, the running therapist discusses experience of exercise in the past, and will provide information about food, moisture balance, fatigue, injuries, sleep and recovery. Patient’s questions about these points can be discussed with the running therapist. The running therapy intervention was conducted at a medical institution (GGZ inGeest) where there is always a physician approachable. Adverse events in both treatment programs will be signalled and reported to the medical ethical committee. So, in all, we (as well as the IRB) believe we have done adequate checks to decide whether (older) patients can contribute to the running therapy intervention. It is also important to emphasize that – based on monitored heart rate – the intensity of the intervention was established. For some persons, fast walking – instead of running - was a starting point in the running therapy as that already gave the maximum heart rate increase. So, the intervention is highly individualized based on an individual’s condition.

We added at page 13: ‘During the screening phase and during baseline assessment, so before formal inclusion in the study, potential physical and/or somatic problems and use of medication are administered. When serious somatic conditions are signalled, the person’s own physician will be contacted and consulted in order to discuss potential study participation. Furthermore, at the beginning of the running intervention, the running therapist discusses experience of exercise in the past, and provides information about food, moisture balance, fatigue, injuries, sleep and recovery. The running therapy intervention was conducted at a medical institution (GGZ inGeest) where there is always a physician approachable.’

We added at page 13: ‘Adverse events in both treatment programs will be signalled and reported to the medical ethical committee.’