nature portfolio

Peer Review File

Effect of exercise therapy and self-management support on multimorbidity: Secondary analysis of the MOBILIZE trial

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for inviting me to review the revised version of this manuscript. I acknowledge the substantial effort the authors have made in addressing the reviewers' comments, and I find their responses to be clear and satisfactory. In particular, the main concerns have been appropriately resolved: the publication of the original RCT provides useful and necessary context, the statistical limitations have been transparently discussed, and the broader implications and impact of this RCT are now more clearly articulated.

Overall, the revisions have considerably strengthened the manuscript. I believe the authors have demonstrated diligence in responding to feedback, and the work is now of sufficient quality to merit publication.

Reviewer #2

(Remarks to the Author)
Brief summary of the manuscript

Thank you for the opportunity to review this study which is presented as a secondary analysis of the MOBILIZE trial. The trial is an important step in research addressing the challenge to support people with multimorbidity. Though it is claimed that this is the first study to show a reduction in systolic blood pressure for people with multimorbidity, the lack of the detail to the exercise dosage is problematic. The reader is made to refer to the main trial for detail to the methods which has proven to be cumbersome. These are other concerns are raised in detail below.

Overall impression of the work

The importance for research to start to address this health problem is made clear in the introduction and the case is made for exercise therapy to be used as an intervention treatment is provided. It is at this point that it would be useful for further detail to be included so that a dose response could be explored. Standardised components of the intervention were prescribed the intervention which also included a "participant's choice segment". This component included the choice between strength, aerobic or functional exercise (20 minutes), however it is unclear how this was recorded. Similarly, it is unclear what the participants adherence or compliance was to the intervention. Finally, it is unclear how important the reduction of systolic blood pressure is in relation to the changes of the other biomarkers not reaching statistical significance.

Specific comments, with recommendations for addressing each comment

Comment 1, page 4 line 68: Please clarify if this relates to type 1 or type 2 diabetes?

Comment 2, page 4 line 78: Exercise therapy has been described to positively influence biomarkers of multimorbidity. This is then followed by several exercise related studies however the type of exercise and the dose response prescribed to achieve these outcomes has not been considered. It is important to present this information as it allows the reader to determine if and how it has been considered in the intervention design. If it has not been considered in the intervention design, it would be necessary to address why.

Comment 3, page 4 last paragraph: It is important to use people first and not reference to the disease “in diabetes” and “In hypertension”

Comment 4, page 9 line 171: further details about the approach used for the self-management skills and motivation, needs to be provided. For example, did this include cognitive behavioural therapy? How long were these sessions? What training was provided to those who delivered the sessions? Was any resources provided to support participants?

Comment 5, page 9 line 173: Given that a prolonged warm up of 15 minutes improves vasodilation for people with selected medical conditions, it is unclear the justification for the warm up in the intervention only being 8 minutes in duration.

Comment 6 relating to the intervention: it is unclear how adherence or compliance to the intervention was monitored and recorded.

Comment 7 relating to the intervention: importantly it is unclear why the participants target heart rate was not monitored and recorded. This is a major concern especially in relation to the study being interested in the changes to biomarkers. In practice, for people on beta-blockers, 20 –30bpm is recommended to be subtracted from the target heart rate to allow this objective method to be used.

Comment 8 relating to the participants characteristics: The interaction of medication that participants may have been prescribed has a significant effect on their exercise capacity and outcomes. Was this detail recorded and considered in the study and analysis?

Comment 9, page 14 line 292: Relating back to a previous point regarding the dose response. As it appears this study did not record intensity using an objective measure such as heart rate, were there any relationship with the exercising RPE and reductions in systolic blood pressure? Importantly, what is the relevance of finding only a significant lowering of systolic blood pressure and not the other biomarkers? Is this the most common risk factor shared amongst the people with multimorbidity?

Comment 10, page 14 line 293: suggests a clinically meaningful result but does not explicitly discuss if it is or is not. Need for clarification.

Comment 11, page 16 line 331: Research implication are not entirely supported by aim and findings of this study. The intervention did not objectively monitor intensity therefore, how is it j

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
Thank you for responding to the feedback and making the relevant amendments. I find the remaining responses to be satisfactory.
Dose response has been sufficiently considered, strengthening the manuscript and provides the reader with a clearer understanding about research on this topic.
Overall, the revisions are acceptable and merit publication.

Point-by-point response letter

Thank you for considering our manuscript for publication in Communication Medicine and for the constructive feedback.

We have adapted the manuscript to the reviewer comments and provided a point-by-point response below in addition to submitting two copies of the manuscript, one with tracked changes and a clean version. The amendments to the manuscript are highlighted in yellow in this response letter and in the manuscript with tracked changes.

We hope you find the manuscript revisions sufficient to merit acceptance, but we appreciate insightful comments and await your future guidance.

On behalf of the authors,

Associate Professor Alessio Bricca

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Thank you for inviting me to review the revised version of this manuscript. I acknowledge the substantial effort the authors have made in addressing the reviewers' comments, and I find their responses to be clear and satisfactory. In particular, the main concerns have been appropriately resolved: the publication of the original RCT provides useful and necessary context, the statistical limitations have been transparently discussed, and the broader implications and impact of this RCT are now more clearly articulated.

Overall, the revisions have considerably strengthened the manuscript. I believe the authors have demonstrated diligence in responding to feedback, and the work is now of sufficient quality to merit publication.

Authors reply: Thank you for the positive feedback on our manuscript.

Reviewer #2 (Remarks to the Author):

Brief summary of the manuscript

Thank you for the opportunity to review this study which is presented as a secondary analysis of the MOBILIZE trial. The trial is an important step in research addressing the challenge to support people with multimorbidity. Though it is claimed that this is the first study to show a reduction in systolic blood pressure for people with multimorbidity, the lack of the detail to

the exercise dosage is problematic. The reader is made to refer to the main trial for detail to the methods which has proven to be cumbersome. These are other concerns are raised in detail below.

Authors reply: Thank you for the feedback on our manuscript. We have now provided additional infomation about the exercise dose as well as the other concerns the reviewer highlighted in the specific responses below.

Overall impression of the work

The importance for research to start to address this health problem is made clear in the introduction and the case is made for exercise therapy to be used as an intervention treatment is provided. It is at this point that it would be useful for further detail to be included so that a dose response could be explored. Standardised components of the intervention were prescribed the intervention which also included a "participant's choice segment". This component included the choice between strength, aerobic or functional exercise (20 minutes), however it is unclear how this was recorded. Similarly, it is unclear what the participants adherence or compliance was to the intervention. Finally, it is unclear how important the reduction of systolic blood pressure is in relation to the changes of the other biomarkers not reaching statistical significance.

Authors reply: Please see below for the specific responses to the comments.

Specific comments, with recommendations for addressing each comment

Comment 1, page 4 line 68: Please clarify if this relates to type 1 or type 2 diabetes?

Authors reply: We have now clarified that it is type 2-diabetes.

Authors action: Line 67: Exercise therapy is a first-line treatment for individuals with single chronic conditions such as type 2-diabetes, osteoarthritis, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, depression, and obesity.

Comment 2: Page 4, line 78: Exercise therapy has been described to positively influence biomarkers of multimorbidity. This is then followed by several exercise related studies however the type of exercise and the dose response prescribed to achieve these outcomes has not been considered. It is important to present this information as it allows the reader to determine if and how it has been considered in the intervention design. If it has not been considered in the intervention design, it would be necessary to address why.

Authors reply: Thank you for these suggestions, which we have now included in the

manuscript.

Authors action: Line 78: Exercise therapy, both aerobic and strengthening, may positively influence biomarkers of multimorbidity through several mechanisms.

Line 86: The dose of exercise that may improve biomarkers of multimorbidity appears high. For instance, in people with type-2 diabetes, the DOSE-EX study showed a signal consistent with beneficial effects on markers of low-grade inflammation only with exercise performed six times per week, but not three times per week.[26] Similarly, the U-TURN trial showed that five to six aerobic sessions per week, over 12 months, at a moderate to high intensity decreased low-grade systemic inflammation but not other biomarkers.[27,28] In contrast, other biomarkers reflecting, for example, glycaemic control and anthropometric outcomes, appear to respond to lower exercise doses, as demonstrated in both the U-TURN and DOSE-EX studies.[29,30] Additionally, a systematic review of RCTs including older adults with at least one chronic condition showed that at least 3 times a week of strength training at ≥70 % of 1 repetition maximum could decrease biomarkers of inflammation.[31] Together, these effects highlight the therapeutic potential of exercise as a core component in the management of complex chronic conditions.[17] Additionally, from a feasibility and implementation perspective, it is crucial to determine whether smaller, more achievable doses than 5–6 sessions per week can still provide meaningful benefits, as this would greatly influence real-world adoption and sustainability.

Line 313: Although the MOBILIZE intervention was not designed to target biomarkers of multimorbidity primarily, and as this secondary analysis was not powered for between-group differences on the biomarkers, we found a statistically significant reduction in systolic blood pressure in the intervention group in addition to usual care as compared to the usual care group alone.

Comment 3, page 4 last paragraph: It is important to use people first and not reference to the disease “in diabetes” and “In hypertension”

Authors reply: Thank you for this suggestion. We have rephrased accordingly.

Authors action: Line 82: For instance, in people with type 2-diabetes…; In people with hypertension…”

Comment 4, page 9 line 171: further details about the approach used for the self-management skills and motivation, needs to be provided. For example, did this include cognitive behavioural therapy? How long were these sessions? What training was provided to those who delivered the sessions? Was any resources provided to support participants?

Authors reply: We have now added details about the self-management sessions to improve clarity. On note, that it did not include cognitive behavioural therapy, but we have mentioned a few of the 24 topics covered in the sessions, which are all reported in detail in the Intervention Development paper and protocol paper.

Bricca, A., Jäger, M., Dideriksen, M. et al. Personalised exercise therapy and self-management support for people with multimorbidity: Development of the MOBILIZE intervention. Pilot Feasibility Stud 8, 244 (2022). https://doi.org/10.1186/s40814-022-01204-y

Skou ST, Nyberg M, Dideriksen M, Overgaard JA, Bodilsen C, Soja AM, Attarzadeh AP, Bieder MJ, Dridi NP, Heltberg A, Gæde PH, Reventlow JL, Arnfred S, Bodtger U, Thygesen LC, Jäger M, Bricca A. Study protocol for a multicenter randomized controlled trial of personalized exercise therapy and self-management support for people with multimorbidity: The MOBILIZE study. J Multimorb Comorb. 2023 Feb 1;13:26335565231154447. https://doi.org/10.1177/26335565231154447

Authors action: Line 182: The programme included 24 supervised exercise sessions (60 minutes/session) and 24 self-management sessions (30 minutes/session), and primarily focused on empowering patients to enhance their ability to engage in their own care more actively. By doing so, the program seeks to reduce symptoms associated with individual conditions, improve quality of life and physical function, and help prevent the onset of additional health problems. The intervention development is described in detail elsewhere.[30,32] Briefly, the self-management support sessions aimed to improve self-management skills and motivation to maintain an active lifestyle and a better quality of life after the program. The sessions covered topics such as sleep, pain management, and physical activity. These modules were designed to equip participants with practical tools to manage life with multiple chronic conditions better.

Comment 5, page 9 line 173: Given that a prolonged warm up of 15 minutes improves vasodilation for people with selected medical conditions, it is unclear the justification for the warm up in the intervention only being 8 minutes in duration.

Authors reply: Thank you for your observation. The MOBILIZE trial was designed as a pragmatic intervention aimed at improving overall health outcomes rather than specifically stimulating molecular adaptations. The exercise protocol followed the ACSM and WHO

guidelines for optimal health benefits in people with multimorbidity. While a 15-minute warm-up may enhance vasodilation in certain medical conditions, the 8-minute warm-up in our intervention was chosen to balance safety, feasibility, and adherence within a real-world setting, often only allowing a total of 60-minute sessions.

Comment 6 relating to the intervention: it is unclear how adherence or compliance to the intervention was monitored and recorded.

Authors reply: We have now clarified how adherence and compliance were monitored and recorded.

Authors action: Line 201: Adherence and compliance were monitored throughout the intervention using diaries, kept at the intervention sites, for exercise therapy (including the "participant's choice segment") and self-management sessions. Adherence was assessed as the number of exercise and self-management support sessions attended out of the total number of sessions available. Compliance was assessed by the patients in the diaries by reporting the rate of perceived exertion in any set of the prescribed program using the OMNI scale for strengthening exercises and the BORG scale for aerobic exercises. The diaries were systematically collected and reviewed by the physiotherapists delivering the intervention to ensure accurate reporting of participation.[35,41]

Comment 7 relating to the intervention: importantly it is unclear why the participants target heart rate was not monitored and recorded. This is a major concern especially in relation to the study being interested in the changes to biomarkers. In practice, for people on beta-blockers, 20 –30bpm is recommended to be subtracted from the target heart rate to allow this objective method to be used.

Authors reply: We agree, but while monitoring target heart rate can provide an objective measure of intensity, it was not implemented because heart rate–based prescriptions reduce practicality in routine care. Instead, intensity was guided by perceived exertion, a widely accepted and feasible approach in pragmatic trials. However, we have now strengthen our research implication section suggesting future studies using device-based methos to monitor intentisy and exertion during exercise.

Authors action: Line 374: Furthermore, future research should examine dose–response relationships and incorporate device-based monitoring such as heart rate sensors, VO2

measurement devices, accelerometers, and smart resistance equipment that allow to record load, repetitions, and velocity during strength training, to accurately capture exercise intensity, exertion, and adherence.

Comment 8 relating to the participants characteristics: The interaction of medication that participants may have been prescribed has a significant effect on their exercise capacity and outcomes. Was this detail recorded and considered in the study and analysis?
Authors reply: Thank you for noting this, which we have clarified in the manuscript.
Authors action: Line 360: The lack of data on changes in medication during the trial, which could either mask a higher intervention effect (if reduced) or explain the observed reduction in blood pressure (if intensified). Although we collected medication information, reporting was highly inconsistent, preventing meaningful classification or subgroup analyses. However, as our participants were randomised and all received the usual care, the risk of this being a significant problem was kept at a minimum.

Comment 9, page 14 line 292: Relating back to a previous point regarding the dose response. As it appears this study did not record intensity using an objective measure such as heart rate, were there any relationship with the exercising RPE and reductions in systolic blood pressure? Importantly, what is the relevance of finding only a significant lowering of systolic blood pressure and not the other biomarkers? Is this the most common risk factor shared amongst the people with multimorbidity?
Authors reply: Thank you for raising these points. Patients exercised at a 'somewhat hard' level using the OMNI scale and moderate intensity on the BORG scale, with supervised sessions ensuring target intensity and minimal RPE variation, precluding meaningful RPE outcome analysis. Although systolic blood pressure was the only biomarker with a statistically significant improvement, it is highly prevalent and clinically relevant in multimorbidity, strongly linked to cardiovascular events and mortality, so even modest reductions are meaningful. Importantly, analyses were not powered for biomarker differences; thus, lack of statistical significance does not equal lack of effect. Most other biomarkers showed patterns consistent with blood pressure, suggesting greater improvements in the intervention group. Hypertension's high prevalence likely explains clearer blood pressure reductions, whereas other biomarkers, despite numerical improvements, were more

heterogeneous, better regulated at baseline, or less responsive within the intervention period.

Authors action: Line 320: Systolic blood pressure decreased 4.7 mm Hg (95% CI -8.8 to -0.6) more in response to exercise therapy and self-management support than usual care alone. A reduction of 5 mm Hg in systolic blood pressure is associated with approximately a 10% decrease in the risk of major cardiovascular events.[44] This reduction also corresponds to decreases in the risk of stroke (13%), heart failure (13%), ischemic heart disease (8%), and cardiovascular death (5%).[44]

Line 354: Finally, hypertension was highly prevalent in our study population,19 making systolic blood pressure a shared and clinically relevant risk factor across conditions. This may aso explain why significant reductions were observed in systolic blood pressure, whereas other biomarkers despite numerical improvements were more heterogeneous, better regulated at baseline, or less responsive within the intervention period.

Comment 10, page 14 line 293: suggests a clinically meaningful result but does not explicitly discuss if it is or is not. Need for clarification.

Authors reply: Thank you for this suggestion, which we have clarified in the manuscript.

Authors action: Line 326: However, given that the 95%CI of the between-group difference covers a reduction smaller than the 5mm Hg, the clinical relevance of our findings needs to be interpreted with caution.

Comment 11, page 16 line 331: Research implication are not entirely supported by aim and findings of this study. The intervention did not objectively monitor intensity therefore, how is it j

Authors reply: Thank you for this comment; We have now clarified in our research implication that future trials should explicitly test higher, objectively monitored exercise doses and their effects on biomarkers.

Authors action: **Line 374:** Furthermore, future research should examine dose–response relationships and incorporate device-based monitoring such as heart rate sensors, VO2 measurement devices, accelerometers, and smart resistance equipment that allow to record load, repetitions, and velocity during strength training, to accurately capture exercise intensity, exertion, and adherence.