Effectiveness of personalized exercise therapy and self-management support in people with multimorbidity on low-grade inflammation, glycaemic control, lipids and blood pressure: protocol for a pre-planned secondary analysis of the MOBILIZE study

AUTHORS

Alessio Bricca[1,2], Mette Nyberg[2], Grit Elster Legaard, [3] Mette Dideriksen,[2] Graziella Zanger[2], Lau C. Thygesen[4], Søren T. Skou [1,2]

AFFILIATIONS

[1] Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, 5230 Odense M, Denmark

[2] The Research and Implementation Unit PROgrez, Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Region Zealand, 4200 Slagelse, Denmark

[3] Centre for Physical Activity Research, Rigshospitalet, Copenhagen, Denmark

[4] National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

CORRESPONDING AUTHOR

Alessio Bricca

Research Unit for Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

Email: abricca@health.sdu.dk

BACKGROUND

Multimorbidity, defined as the co-occurrence of two or more chronic conditions, poses a significant health burden globally, affecting a third of the adult population.[1] Individuals with multimorbidity experience complex health challenges, including increased risk of disability, reduced quality of life, and increased healthcare costs.[2-4] Additionally, multimorbidity is associated with elevated levels of systemic inflammation, impaired glycaemic control, lipids cholesterol, and blood pressure, which are linked to accelerated progression of chronic conditions and premature mortality.[4-11]

Systematic reviews have shown that exercise therapy appears safe and beneficial for people with multimorbidity.[12,13] Additionally, our recent trial has demonstrated that personalized exercise therapy, combined with self-management support, can have positive long-term effects on health-related quality of life in people with multimorbidity.[14] These interventions help people manage their health more proactively and underscore their potential to also mitigate the underlying inflammatory, metabolic, and symptomatic processes that contribute to poor health outcomes in this population.[1]

While cross-sectional studies have shown an association between physical activity and lower levels of inflammatory biomarkers in people with multimorbidity,[15,16] it remains unclear if increased physical activity in the form of a structured exercise therapy intervention can achieve similar effects. Additionally, trials including people with single chronic conditions such as diabetes, hypertension, and obesity have shown that exercise therapy can improve glycaemic control, cholesterol, and blood pressure, [17-19] but evidence on people with multimorbidity is lacking.[1] Therefore, in this pre-planned secondary analysis of the MOBILIZE trial, we aim to explore whether a personalized exercise therapy and self-management program, compared to usual care, can reduce low-grade systemic inflammation, glycaemic control, cholesterol, and blood pressure.

METHODS

The RCT protocol has been published elsewhere,[20] and the statistical analysis plan for the main trial is available for download at https://findresearcher.sdu.dk/ws/portalfiles/portal/260212804/SAP_MOBILIZE_final.pdf. ClinicalTrials.gov registration: NCT04645732. Data in the MOBILIZE trial were assessed at baseline, 4 months (approx. 16 weeks; immediately after the treatment program), 6 months and 12 months after randomization. This pre-planned secondary analysis includes data from the baseline and 4-month assessment, where the molecular biomarkers were collected.

Interventions

Briefly, the MOBILIZE RCT investigates the effects of personalized exercise therapy and self-management support in addition to usual care in patients with multimorbidity. 228 participants were randomized (1:1) to a 12-week intervention in addition to usual care or usual care alone. The program comprised 24 supervised exercise sessions (60 minutes/session) and 24 self-management sessions (30 minutes/session).Detailed descriptions of the program, including the co-development phase involving various stakeholders, and significant patient and carer participations, are available elsewhere[20,21]

Outcomes

Objectively measured outcomes

Molecular biomarkers were collected at baseline and 4 months (approx. 16 weeks; immediately after the treatment program).[20] The participants were informed to fast by not eating or drinking anything except water for 10 hours before the test. Concentration of the following molecular biomarkers will be included: Interleukin-1 receptor antagonist (IL-1ra pg/ml), high-sensitivity C-reactive protein (hs-CRP pg/ml), Tumor necrosis factor (TNF pg/ml), Interleukin 6 (IL-6 pg/ml), High-Density Lipoprotein (HDL) cholesterol (mmol/l) and Low-Density Lipoprotein (LDL) cholesterol (mmol/l), triglycerides (mmol/l), HbA1c (pg/ml), fasting glucose (mmol/l) and fasting insulin (mUL/L). The samples were stored at the local Departments of Clinical Biochemistry in Holbæk, Roskilde, Næstved, Slagelse, Nykøbing Falster and at Rigshospitalet in Copenhagen. Fasting plasma samples were centrifuged and stored at -80 ◦C until analyses. They were measured using immunoassay kits from Meso Scale Discovery, USA, as follows: IL-1Ra (V-PLEX Cytokine Panel 2 (human) kit), CRP (V-PLEX vascular injury Panel 2 (human) kit), TNFα and IL-6 (V-PLEX Proinflammatory Panel1(human)). Systolic and diastolic blood pressures after 5 minutes of rest were measured as the mean of three consecutive measurements using the Rossmax X5 blood pressure monitor (Rossmax, Heerbrugg, Switzerland) at baseline and 4-month follow-up. Participants were asked to avoid smoking, consuming alcohol, or drinking coffee for half an hour before the blood pressure measurement

Randomization procedure and blinding

Participants who met the eligibility criteria and signed the informed consent form were randomized in a 1:1 allocation ratio following baseline assessment. The statistician had previously prepared a computer-generated randomization schedule using permuted blocks of four or six individuals, stratified by the number of chronic conditions (2 or 3+) and by recruitment centres. Allocation numbers were concealed in opaque sealed envelopes, which were only accessible to a study coordinator after informed consent and baseline assessment were completed. Only outcome assessors and the statistician were blinded to randomization.

Sample size and hypothesis

Sample size was determined for the main primary analysis reported separately.[20] This study presents an exploratory analysis. 95% confidence intervals are reported throughout to show a precision of the estimates. We hypothesized the exercise therapy and self-management group to reduce molecular biomarkers related to inflammation, glycaemic control, lipids, and blood pressure to a greater extent than the usual care group.

Statistical analysis

Between-group comparisons of change from baseline to the follow-up at 4 months in continuous outcomes will be analysed using repeated measures mixed-effects linear model, in line with the analysis of the primary report.[20] Participants will be included as a random effect thereby assuming that missing data is missing at random. Visits (baseline and 4 months), treatment arm (Exercise therapy and self-management support program versus Usual care), and interaction between the 4 months visit and treatment arm will be included as fixed effects. The interaction term is the main test of effect. The model will be adjusted for the randomization stratification factors (number of chronic conditions (2 or 3+) and recruitment center (hospitals, general practitioners, and self-referrals)) by including them as fixed effects. MOCK Table 1 illustrates how the results will be presented in the manuscript.

All randomized participants with at least a valid assessment of the outcomes of interest will be included in the primary analysis. In the per-protocol analysis, the following participants will be excluded: 1) participants in the exercise and self-management group participating in less than 18 out of the 24 self-management and exercise sessions (this was a pre-defined threshold chosen to deem the attendance to the intervention satisfactory); 2) participants in both groups experiencing serious adverse events such as hospitalization or surgery during the 4-month follow-up, 3) participants who had undergone major surgeries and/or were hospitalized for more than 7 consecutive days during the 4-month follow-up.

Dissemination and protocol amendments

The results, regardless of whether they are in favor of the intervention or comparator group or inconclusive in relation to the study hypothesis, will be communicated in scientific papers, at relevant conferences, to a broader audience in the news and social media, through online support tools including multimedia and print education resources, in oral presentations and popular science magazines. Authorship eligibility will be based on the recommendations from the International Committees of Medical Journal Editors (ICMJE).

Acknowledgments

We would like to thank Gregers Aagaard, Margit Dybkjær, Flemming Tage Jensen, Elin Nielsen, Kaj Johansen and Bitten Christensen, who all live with multimorbidity, as well as Tue Dybkjær, Lonni Heidelbach and Klaus Heidelbach, who provide care and support to family members with multimorbidity, for their feedback on MOBILIZE, including study design, methods and conduct. We would also like to thank the recruitment centres, healthcare providers, and persons involved in the study conduct. Finally, we owe gratitude to the MOBILIZE scientific advisory board consisting of Prof. Susan Smith, Prof. Sallie Lamb, Prof. Alan Silman, Prof. Bente Klarlund Pedersen, Prof. Ewa M. Roos, and Prof. Rod Taylor.

Conflicts of interests

STS has received personal fees from Munksgaard, TrustMe-Ed and Nestlé Health Science, all of which are outside the submitted work. He is co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aiming at implementing clinical guidelines for persons with osteoarthritis in clinical practice. AB has received personal fees from TrustMe-Ed and PhisioVis srl, both of which are outside the submitted work.The authors declare that there is no other conflict of interest.

Funding

The present study was supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (MOBILIZE; grant agreement No 801790), a research program grant from Region Zealand (Exercise First), Næstved, Slagelse and Ringsted Hospitals' Research Fund, The Danish Regions and The Danish Health Confederation through the Development and Research Fund (project no. 2703) and The Association of Danish Physiotherapists Research Fund. Furthermore, STS is the recipient of an ongoing, unrelated grant from the European Union's Horizon 2020 research and innovation program (ESCAPE; grant agreement No 945377).

References

1 Skou, S. T. *et al.* Multimorbidity. *Nature Reviews Disease Primers* **8**, 48, doi:10.1038/s41572-022-00376-4 (2022).
2 Makovski, T. T., Schmitz, S., Zeegers, M. P., Stranges, S. & van den Akker, M. Multimorbidity and quality of life: Systematic literature review and meta-analysis. *Ageing Res Rev* **53**, 100903, doi:10.1016/j.arr.2019.04.005 (2019).
3 McPhail, S. M. Multimorbidity in chronic disease: impact on health care resources and costs. *Risk Manag Healthc Policy* **9**, 143-156, doi:10.2147/RMHP.S97248 (2016).
4 Nunes, B. P., Flores, T. R., Mielke, G. I., Thume, E. & Facchini, L. A. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr* **67**, 130-138, doi:10.1016/j.archger.2016.07.008 (2016).
5 Gregg, E. W. *et al.* The burden of diabetes-associated multiple long-term conditions on years of life spent and lost. *Nature Medicine* **30**, 2830-2837, doi:10.1038/s41591-024-03123-2 (2024).
6 Tran, J. *et al.* Multi-morbidity and blood pressure trajectories in hypertensive patients: A multiple landmark cohort study. *PLOS Medicine* **18**, e1003674, doi:10.1371/journal.pmed.1003674 (2021).

7 Han, S. *et al.* Mapping multimorbidity progression among 190 diseases. *Communications Medicine* **4**, 139, doi:10.1038/s43856-024-00563-2 (2024).
8 Goërtz, Y. M. J. *et al.* Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study. *Scientific Reports* **11**, 20977, doi:10.1038/s41598-021-00337-z (2021).
9 Stylianou, E. Epigenetics of chronic inflammatory diseases. *J Inflamm Res* **12**, 1-14, doi:10.2147/JIR.S129027 (2019).
10 Schottker, B., Saum, K. U., Jansen, E. H., Holleczek, B. & Brenner, H. Associations of metabolic, inflammatory and oxidative stress markers with total morbidity and multi-morbidity in a large cohort of older German adults. *Age Ageing* **45**, 127-135, doi:10.1093/ageing/afv159 (2016).
11 Scherer, M. *et al.* Association between multimorbidity patterns and chronic pain in elderly primary care patients: a cross-sectional observational study. *BMC Fam Pract* **17**, 68, doi:10.1186/s12875-016-0468-1 (2016).
12 Bricca, A. *et al.* Benefits and harms of exercise therapy in people with multimorbidity: A systematic review and meta-analysis of randomised controlled trials. *Ageing Res Rev* **63**, 101166, doi:10.1016/j.arr.2020.101166 (2020).
13 Bricca, A. *et al.* Effect of In-Person Delivered Behavioural Interventions in People with Multimorbidity: Systematic Review and Meta-analysis. *Int J Behav Med* **30**, 167-189, doi:10.1007/s12529-022-10092-8 (2023).
14 Skou, S. T. *et al.* Exercise therapy and self-management support for individuals with multimorbidity: The MOBILIZE multicenter, randomized, controlled trial. *(under review)* (2024).
15 Cheng, W., Du, Z. & Lu, B. Chronic low-grade inflammation associated with higher risk and earlier onset of cardiometabolic multimorbidity in middle-aged and older adults: a population-based cohort study. *Scientific Reports* **14**, 22635, doi:10.1038/s41598-024-72988-7 (2024).
16 Poulsen, V. R. *et al.* The association between physical activity, low-grade inflammation, and labour market attachment among people with multimorbidity: A cross-sectional study from the Lolland-Falster Health Study, Denmark. *J Multimorb Comorb* **13**, 26335565231195510, doi:10.1177/26335565231195510 (2023).
17 Dibben, G. O. *et al.* Evidence for exercise-based interventions across 45 different long-term conditions: an overview of systematic reviews. *eClinicalMedicine* **72**, doi:10.1016/j.eclinm.2024.102599 (2024).
18 Ostman, C. *et al.* The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a systematic review and meta-analysis. *Cardiovascular Diabetology* **16**, 110, doi:10.1186/s12933-017-0590-y (2017).
19 Naci, H. *et al.* How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med* **53**, 859-869, doi:10.1136/bjsports-2018-099921 (2019).
20 Skou, S. T. *et al.* 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* **13**, 26335565231154447, doi:10.1177/26335565231154447 (2023).
21 Bricca, A. *et al.* Personalised exercise therapy and self-management support for people with multimorbidity: Development of the MOBILIZE intervention. *Pilot Feasibility Stud* **8**, 244, doi:10.1186/s40814-022-01204-y (2022).

Mock table 1.

Outcome	**Total no. of assessments**	**Mean score at 4 months in the exercise therapy and self-management group**	**Mean score at 4 months in the usual care group**	**Change from baseline to 4 months in the exercise therapy and self-management group**	**Change from baseline to 4 months in usual care group**	**Between-Group difference in mean improvement (crude) (95% CI)**	**Between-Group difference in mean improvement (adjusted)[2] (95% CI)**
Interleukin-1 receptor antagonist (IL-1ra pg/ml)							
High-sensitivity C-reactive protein (hs-CRP pg/ml)							
Tumor necrosis factor (TNF pg/ml)							
Interleukin 6 (IL-6 pg/ml)							

High Density Lipoprotein (HDL) cholesterol (mmol/l)							
Low Density Lipoprotein (LDL) cholesterol (mmol/l)							
Triglycerides (mmol/l)							
HbA1c (pg/ml)							
Fasting glucose (mmol/l)							
Fasting insulin (mUL/L)							
Systolic blood pressure							

Diastolic blood pressure							

[2] Adjusted for the randomization stratification factors (number of chronic conditions (2 or 3+) and recruitment centre (hospitals, general practitioners, and self-referrals)) by including them as fixed effects

Supplementary files

Effect of exercise therapy and self-management support on biomarkers of multimorbidity

Secondary analysis of the MOBILIZE trial

Alessio Bricca[1,2], Mette Nyberg[2], Grit Elster Legaard, [3] Mette Dideriksen,[2] Graziella Zanger[2], Lau C. Thygesen[4], Søren T. Skou [1,2]

[1] Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, 5230 Odense M, Denmark

[2] The Research and Implementation Unit PROgrez, Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Region Zealand, 4200 Slagelse, Denmark

[3] Centre for Physical Activity Research, Rigshospitalet, Copenhagen, Denmark

[4] National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

Table of Contents

Supplementary Table 1. Sensitivity analysis including individuals that completed at least (75%) 18 out of the 24 sessions available (N=86).

Outcome	**Between-Group difference in mean improvement (crude) (95% CI)**	**Between-Group difference in mean improvement (adjusted)[2] (95% CI)**
Interleukin-1 receptor antagonist (pg/ml)	-48.5 (-118.4 to 21.3)	-48.9 (-118.8 to 21.0)
High-sensitivity C-reactive protein (pg/ml)	-2.04 (-4.88 to 0.80)	-2.03 (-4.87 to 0.80)
Tumor necrosis factor (pg/ml)	-0.02 (-0.18 to 0.13)	-0.02 (-0.18 to 0.14)
Interleukin 6 (pg/ml)	-0.43 (-1.24 to 0.37)	-0.43 (-1.24 to 0.37)
High Density Lipoprotein cholesterol (mmol/l)	-0.0003 (-0.06 to 0.06)	-0.0006 (-0.06 to 0.06)
Low Density Lipoprotein cholesterol (mmol/l)	-0.05 (-0.21 to 0.11)	-0.05 (-0.21 to 0.11)
Cholesterol (total from plasma) (mmol/l)	-0.07 (-0.25 to 0.11)	-0.07 (-0.25 to 0.11)
Triglycerides (mmol/l)	-0.10 (-0.28 to 0.08)	-0.10 (-0.28 to 0.08)
HbA1c (pg/ml)	-0.69 (-2.06 to 0.67)	-0.69 (-2.06 to 0.67)
Fasting glucose (mmol/l)	-0.09 (-0.28 to 0.11)	-0.09 (-0.28 to 0.11)
Fasting insulin (mUL/L)	1.66 (-3.05 to 6.37)	1.64 (-3.06 to 6.36)
Systolic blood pressure (mmHg)	-5.01 (-9.22 to -0.80)	-5.03 (-9.24 to -0.82)
Diastolic blood pressure (mmHg)	-2.61 (-5.85 to 0.63)	-2.67 (-5.90 to 0.56)

[2] Adjusted for the randomization stratification factors (number of chronic conditions (2 or 3+) and recruitment centre (hospitals, general practitioners, and self-referrals)) by including them as fixed effects; SD =standard deviation; mmHg= millimetres of mercury.

Supplementary Table 2. Sensitivity analysis without individuals (n=11) in the usual care group that received supervised exercise therapy sessions or individuals that in both groups undergo surgery in the 4-month follow up.

Outcome	Between-Group difference in mean improvement (crude) (95% CI)	Between-Group difference in mean improvement (adjusted)[2] (95% CI)
Interleukin-1 receptor antagonist (pg/ml)	-36.9 (-105.1 to 31.1)	-37.5 (-105.7 to 30.6)
High-sensitivity C-reactive protein (pg/ml)	-0.93 (-3.72 to 1.87)	-0.92 (-3.71 to 1.87)
Tumor necrosis factor (pg/ml)	-0.02 (-0.17 to 0.13)	-0.02 (-0.17 to 0.13)
Interleukin 6 (pg/ml)	-0.21 (-0.99 to 0.56)	-0.22 (-0.99 to 0.55)
High Density Lipoprotein cholesterol (mmol/l)	0.02 (-0.04 to 0.09)	0.02 (-0.04 to 0.09)
Low Density Lipoprotein cholesterol (mmol/l)	-0.11 (-0.31 to 0.08)	-0.11 (-0.31 to 0.08)
Cholesterol (total from plasma) (mmol/l)	-0.11 (-0.31 to 0.09)	-0.11 (-0.31 to 0.09)
Triglycerides (mmol/l)	-0.10 (-0.29 to 0.08)	-0.10 (-0.29 to 0.08)
HbA1c (pg/ml)	-0.89 (-2.18 to 0.39)	-0.89 (-2.17 to 0.39)
Fasting glucose (mmol/l)	-0.11 (-0.29 to 0.08)	-0.11 (-0.29 to 0.08)
Fasting insulin (mUL/L)	1.79 (-2.72 to 6.31)	1.76 (-2.76 to 6.28)
Systolic blood pressure (mmHg)	-5.13 (-9.35 to -0.91)	-5.20 (-9.42 to -0.98)
Diastolic blood pressure (mmHg)	-2.54 (-5.70 to 0.62)	-2.69 (-5.84 to 0.47)

[2] Adjusted for the randomization stratification factors (number of chronic conditions (2 or 3+) and recruitment centre (hospitals, general practitioners, and self-referrals)) by including them as fixed effects; SD =standard deviation; mmHg= millimetres of mercury.

Supplementary Table 3. Sensitivity analysis with imputed data for the biomarkers of interest.

Outcome	Between-Group difference in mean improvement (crude) (95% CI)	Between-Group difference in mean improvement (adjusted)[2] (95% CI)
Interleukin-1 receptor antagonist (pg/ml)	-40.7 (-105.7 to 24.3)	-41.1 (-106.1 to 23.9)
High-sensitivity C-reactive protein (pg/ml)	-1.56 (-4.29 to 1.18)	-1.55 (-4.29 to 1.19)
Tumor necrosis factor (pg/ml)	-0.03 (-0.26 to 0.20)	-0.03 (-0.18 to 0.12)
Interleukin 6 (pg/ml)	-0.30 (-1.06 to 0.45)	-0.31 (-1.06 to 0.44)
High Density Lipoprotein cholesterol (mmol/l)	0.01 (-0.05 to 0.07)	0.01 (-0.05 to 0.07)
Low Density Lipoprotein cholesterol (mmol/l)	-0.11 (-0.30 to 0.08)	-0.11 (-0.29 to 0.08)
Cholesterol (total from plasma) (mmol/l)	-0.11 (-0.30 to 0.09)	-0.11 (-0.30 to 0.09)
Triglycerides (mmol/l)	-0.09 (-0.27 to 0.09)	-0.09 (-0.27 to 0.09)
HbA1c (pg/ml)	-0.70 (-2.00 to 0.60)	-0.70 (-2.00 to 0.60)
Fasting glucose (mmol/l)	-0.08 (-0.27 to 0.11)	-0.08 (-0.27 to 0.10)
Fasting insulin (mUL/L)	1.72 (-2.58 to 6.01)	1.71 (-2.58 to 6.01)
Systolic blood pressure (mmHg)	-4.64 (-8.74 to -0.55)	-4.73 (-8.82 to -0.64)
Diastolic blood pressure (mmHg)	-2.23 (-5.29 to 0.82)	-2.39 (-5.45 to 0.66)

[2] Adjusted for the randomization stratification factors (number of chronic conditions (2 or 3+) and recruitment centre (hospitals, general practitioners, and self-referrals)) by including them as fixed effects; SD =standard deviation; mmHg= millimetres of mercury.