Physical Function of Older Citizens During Municipality-based Rehabilitation - Statistical Analysis Plan

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Roles and responsibility:

Sanel Teljigović, Ph.D. student, ***principal investigator***
Center for Nutrition and Rehabilitation, Department of Physiotherapy, University College Absalon, Parkvej 190, 4700 Næstved, Denmark &
Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.
sate@pha.dk / steljigovic@health.sdu.dk

Louise Fleng Sandal, assistant professor, ***supervisor***
Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.
lsandal@health.sdu.dk

Tina Dalager, assistant professor, ***supervisor***
Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.
tdalager@health.sdu.dk

Nina Odgaard Nielsen, associate professor, ***supervisor***
Center for Nutrition and Rehabilitation, Department of Physiotherapy, University College Absalon.
nion@pha.dk

Lars Holm, professor, ***supervisor***
School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK.
L.Holm@bham.ac.uk

Gisela Sjøgaard, professor emeritus, ***supervisor***
Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.
gsjogaard@health.sdu.dk

Karen Søgaard, professor, ***principal supervisor***
Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.
ksogaard@health.sdu.dk

*This statistical analysis plan is based on the SAP guidelines presented by Gamble et al.(1)

Introduction

When choosing outcomes to assess the effectiveness of a physical rehabilitation program, it is essential to consider the constructs being measured and their value to the patient and the psychometric properties. Choosing an outcome that reflects all aspects of International Classification levels of Functioning, Disability and Health (ICF) is challenging, especially in heterogeneous groups. However, it is important to know the psychometric properties as this gives important knowledge on how to interpret results and, consequently, how this can inform the patient's care.

The Short Musculoskeletal Function Assessment (SMFA) questionnaire can reflect differences in patients' functional status with a broad range of disorders, like for older citizens undergoing municipality-based physical rehabilitation. This is also why we have chosen the SMFA as the primary outcome in our randomized controlled trial (2).

Nevertheless, since there is no golden standard to measure physical rehabilitation outcomes, construct validity needs to be established to investigate how scores of SMFA can be related to measures on all levels of ICF.

Objectives

Therefore, this cross sectional study on older citizens referred to municipality-based rehabilitation has three main objectives:

1. To investigate how scores of the SMFA questionnaire are related to measures on different ICF levels
2. To describe the characteristics of older citizens starting municipality-based rehabilitation on all ICF levels
3. To investigate predictor variables of upper- and lower extremity strength

Study methods

Trial design

This study was designed as a descriptive observational cross-sectional study.

Sample size

The sample size references the number of participants to include in the study to answer the first objective regarding construct validity. To detect a correlation coefficient of minimum r=+/-0.3 with a significance level of 0.05 and power of 0.8 between the primary outcome SMFA and the generic health-related quality of life questionnaire SF36, a minimum of 85 participants were needed based on the Fisher's z test. Some studies have shown a response rate for the SMFA to be approximately 65% in cross sectional studies (3). We, therefore, added another 35% extra participants to the calculated sample size, resulting in a target of 115 participants to be initially included in the study.

Statistical principles

P-values and statistical significance

A two-tailed probability value of $p \leq .05$ will be considered statistically significant, and estimates will also be presented with 95% confidence intervals.

Descriptive statistics

Descriptive data and fitted regression residuals from linear regression models will be inspected visually for Gaussian distribution by QQ-plots and frequency histograms and tested statistically with the Shapiro-Wilk test. Parametric and/or non-parametric statistical analysis will be used appropriately. Where appropriate, variables will be summarized by means and standard deviations, otherwise as medians with interquartile ranges. Categorical data will be summarized using counts and percentages.

Correlations

Pearson correlation coefficient and Spearman's Rank-Order correlation will be used based on the fulfilment of assumptions.
Correlation coefficients between r=.1-.25 represent a weak correlation, r=.25-.50 a fair correlation, r=.5-.75 a moderate correlation and above r=.75 a strong correlation (4).

Regression models

Mixed linear and quantile regression models will be used based on the fulfilment of assumptions.

Subgroup analysis/exploratory analysis

Since the targeted population might vary considerably for their primary reason of referral to rehabilitation, participants will be divided into clinically meaningful subgroups: Lower extremity disorders, upper extremity disorders, spinal disorders.

Trial population

Screening data

Screening data has been logged. Age, gender, reason for referral to physical rehabilitation and reason for exclusion is available to describe representativeness of the included population.

Target group

115 men and women from Slagelse municipality's community-based health centre were recruited in the period January 2021- Sept 2021 (Fig. 1 – Flow chart).

Eligibility

Inclusion Criteria

All citizens that were referred to the health/rehabilitation center aged ≥ 65 years from Slagelse municipality were invited to a screening interview with a physiotherapist after which the participant was asked to join the study if not subject to one of the following exclusion criteria's:

Exclusion Criteria:

- Inability to speak or read Danish,
- Active cancer,
- Upper or lower limb amputations,
- Hypertension >180/90,
- Referred to rehabilitation primarily due to gynecological or neurological conditions (apoplexies) or surgeries where movement restrictions prohibit participating in most of the tests,
- Discouragement from a general practitioner

Recruitment

Fig. 1 - Flow Chart "EXAMPLE"

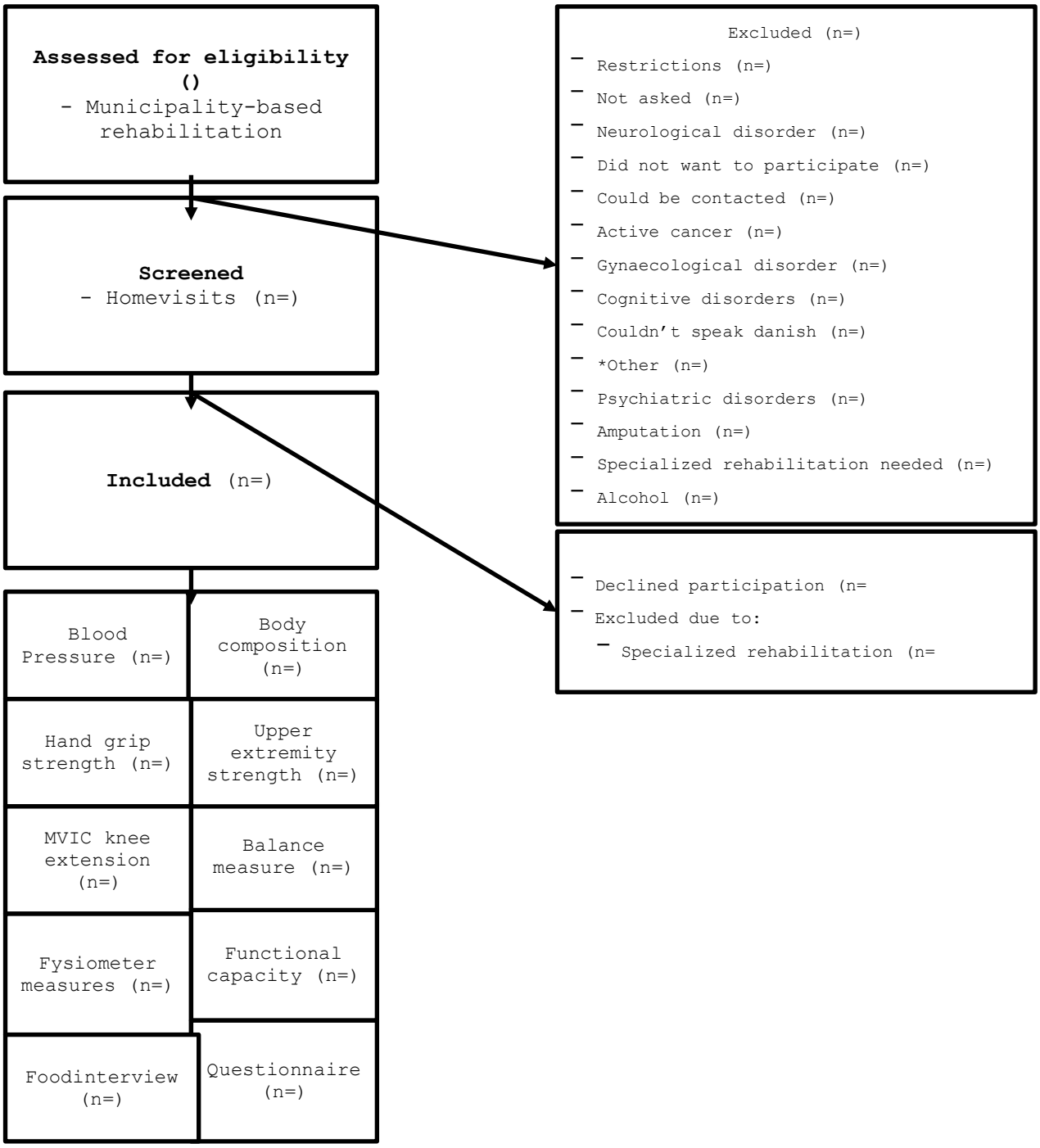

Fig.1: Flow chart of recruitment process.
* Other indicate complex health issues that excluded the patients from participating in most of the selected tests (< 50% of the tests).

Participant characteristics

Table 1 – Characteristics of the participants

Gender, male/female, n(%)	
Age, years	
	65-79
	≥ 80
Weight, kg.	
BMI, kg/m^2	
Clinical groups, n(%)	
	Lower extremity
	Upper extremity
	Spinal
Primary reason of referral, n(%)	
Comorbidities, n(%)	
	0
	1-2
	2-3
	>4
Medication, n(%)	
Level of education completed, n(%)	
	Primary school
	Secondary school
	Higher education
Living alone, Yes/No, n(%)	
Annual income, n(%)	
Physical activity level, n(%)	
	Sedentary
	Standing or walking, without physical exertion
	Standing or walking with several lifting or carrying activities
	Strenuous physical activities

Gaussian distributed data is presented as means ± SD, otherwise as medians with interquartile range.

Lower extremity clinical group definition:

Upper extremity clinical group definition:

Spinal clinical group definition:

Analysis

Outcome definitions

Primary outcome	**Assessing**	**Instrument / equipment**
Short Musculoskeletal Function Assessment (SMFA) Scores for the SMFA is divided in a dysfunction index SMFA-D and a bother index SMFA-B.	Functional status.	Self-reported Questionnaire
Secondary outcome		
Short Form 36 (SF-36)	Health-related quality of life.	Self-reported Questionnaire
Other outcome measures		
The New Mobility Score (NMS): composed score of physical mobility. Each question is scored between 0-3 points, depending on the degree of help. The total possible score is between 0 and 9 points. Higher scores indicate better mobility.	Walking function inside, outside, and during shopping. Including whether a walking aid is used.	Self-reported Questionnaire
PRISMA-7: composed score of frailty - each question scores either 0 or 1 points. The total possible score is between 0 and 7 points. Lower scores indicate less frailty.	Frailty/risk of frailty.	Self-reported Questionnaire

Tilburg Frailty Indicator (TFI): bio-psycho-social approach, which measures frailty. It is composed of 15 multidimensional questions, regarding the physical, psychological, and social aspects of human functioning. Scoring range is between 0-15 points.	Frailty/risk of frailty.	Self-reported Questionnaire
A survey with *self-formulated questions* regarding name, sex, personal ID (CPR number), educational level, the region of pain the last three months (marked on a body chart), pain intensity and pain duration at the most painful body region the last three months, and physical activity level.	Musculoskeletal pain (region of pain, intensity of pain, duration of pain), physical activity level and demographic information.	Self-reported Questionnaire
Weight	Weight in kilograms.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Height	Height in meters.	Etopoo stadiometer (China)
Blood pressure	Systolic and diastolic blood pressure in mmHg.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Resting heart rate	Resting heart rate in beats per minute (BPM).	Omron HBP 1100 (Omron, Kyoto, Japan)

Lean body mass	Total and segmental lean body mass in kilograms.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Fat percentage	Total and segmental body fat in percent of the total body mass.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Total body water	Total body water in percent of the total body mass.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Visceral fat score on a scale ranging between 1-59.	Visceral fat level	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)
Basic metabolic rate (BMR)	BMR in kilojoules.	Tanita 9MC-780U Multi Frequency Segmental Body Composition Analyzer (Tanita, Tokyo, Japan)

Waist-To-Hip ratio	Distribution of fat and overall health. The waist-To-Hip ratio is calculated by measuring the circumference of the waist (in centimeters) and dividing it with the circumference of the hip (in centimeters) to report the Waist-to-hip ratio.	Non elastic plastic measuring tape (Producent not specified)
Maximal torque in knee extension	Maximal isometric strength in knee extension (MVIC). The MVIC will be calculated by multiplying produced force and the length of the moment arm.	Strain gauge (SDU, Odense, Denmark)
Handgrip strength	Maximal isometric strength of handgrip.	SAEHAN hydraulic dynamometer (Saehan, Masan, South Korea)
Shoulder strength	Shoulder abduction strength in kilograms using a handheld dynamometer.	MicroFET2 (Utah, USA)
Elbow strength	Elbow flexion and extension strength in kilograms using a handheld dynamometer.	MicroFET2 (Utah, USA)

Statistical Analysis Plan

Leg press strength	Five repetitions maximum strength test in leg press in kilograms.	Technogym training equipment (Technogym, Cesena, Italy)
Knee extension strength	Five repetitions maximum strength test in knee extension in kilograms.	Technogym training equipment (Technogym, Cesena, Italy)
Calf extension strength	Five repetitions maximum strength tests in calf extension in kilograms.	Technogym training equipment (Technogym, Cesena, Italy)
2-minute walk test	Gait speed and distance. Gait speed will be calculated by dividing the covered distance with the time in seconds. Heart rate (in BPM) and perceived exertion (BORG 6-20) are collected pre- and post-testing.	Course 15.2 meters Stopwatch Apple Watch series 5 The Borg Rating of Perceived Exertion 6-20 scale
Timed Up and Go test (TUG)	Time noted in seconds on how long it takes to get up from a chair, walk three meters, turn around and go back to the chair and sit down again.	Course 3 meters Chair (46 centimeters in height) with armrests Stopwatch
Tandem test	Static balance Balance is tested in three positions for ten seconds each (feet together,	Stopwatch

	semi tandem, and full tandem). Time is noted in seconds for how long the participant can stand in each position.	
Balance test and reaction test for upper and lower extremities	<u>Balance test:</u> Velocity of the center of pressure in mm/sec. Ellipse area for the center of pressure in mm^2. <u>Reaction test:</u> Average reaction time in milliseconds (ms) of seven reaction tests.	Fysiometer software (Brønderslev, Denmark) Nintendo Wii Balance Board (Kyoto, Japan)
Food interviews	Intake of total energy intake and macronutrients based on 24-hour dietary recall interviews.	Vitakost software (Kolding, Denmark)
History of falls	Interview regarding history of fall within the last year	Interview

Analysis methods

- *For objective 1:*
  - Under the assumption of normally distributed data, Pearson correlation coefficients will be calculated and presented with p values and 95%CI. Otherwise as Spearman's rank order correlation coefficients.
  - Correlations will be conducted between SMFA-D/SMFA-B and measures on different ICF levels:
    - SMFA-D/SMFA-B and clinical measures *(upper extremity strength, lower extremity strength, body composition, gait test, TUG test, balance tests, reaction tests)*.
    - SMFA-D/SMFA-B and other questionnaires *(SF36 health survey, Tilburg Frailty Indicator, PRISMA-7, and NMS)*.
  - Cronbach's alpha will be calculated to investigate the internal consistency of the specific categories of the SMFA *(daily activities, emotional status, arm and hand function category, mobility). Cronbach's alpha above .70 are usually acceptable(5).*
    - Under the assumption of acceptable Cronbach's alpha values, same correlations will be conducted between specific categories of the SMFA and the different levels of ICF.
  - Under assumption of normally distributed data, two tailed unpaired t-tests will be conducted to investigate differences in SMFA-D/SMFA-B scores and presented baseline characteristics. Otherwise, a Mann-Whitney U test will be conducted.
- *For objective 2:*
  - Under the assumption of normally distributed data, summary statistics will be presented as means with standard deviations, otherwise as medians with interquartile ranges. Categorical data will be presented with counts and percentages.
  - Summary statistics will be presented for the total sample and for each clinical group.
- *For objective 3:*
  - Under the assumption of normally distributed data, linear regression models will be conducted to investigate whether handgrip strength can be a predictor/proxy of upper extremity strength. Otherwise, quantile regression models will be conducted.

- Upper extremity strength measures (elbow extension, elbow flexion, shoulder abduction) will be set as the dependent variable and hand grip strength of the same arm as the predictor variable. Other explanatory variables to be fitted in the model will be: *age, gender, and height* since these variables affect hand grip strength(6). Other variables added in the model are the fat free mass and knee extension strength(7).

Hypothesis

- SMFA-D and SMFA-B are strongly correlated with each other(8).
- SMFA-D and SMFA-B scores are fair to moderately negatively correlated with the following clinical measures: handgrip strength, MVIC of knee extension, tandem balance test, 2-minute walk test, Leg press strength, knee extension strength and calf extension strength.
  Further, we hypothesize that the SMFA-D will show higher negative correlations with mentioned clinical measures than the SMFA-B (8).
- SMFA-D and SMFA-B are moderate to highly correlated with other health-related questionnaires and frailty indicators: SF36 (negative association), Tilburg Frailty Indicator (positive association), PRISMA7 (positive association) and NMS (positive association) (9, 10).
- We hypothesize that specific functional areas on the SMFA will not be as strongly related to the sum score of SMFA as they will be to a specific category (8).
- We anticipate low physical and functional scores of the total sample (11).
- Handgrip strength is a good proxy of upper extremity strength (elbow extension, elbow flexion and shoulder abduction)(12).

Missing data

- We do not expect missing values to be greater than 5 percent for the SMFA, besides the sexual activity question (8). Scoring instructions for the SMFA will be followed, and missing responses will be handled as suggested by the original authors (13).
- We anticipated that some participants would not complete all clinical tests due to discomfort, pain, or fear of injury. In these circumstances, those participants will be excluded from the specific analysis.

Statistical software

Data will be analyzed using StataBE ver. 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.).

Protocol deviations

Minor adjustments were made after trial registration on Clinicaltrials.gov.

- Due to the COVID19 lockdown, some facilities in the municipality were closed. We, therefore, needed to adjust the testing setup for some tests.
  - The course for the 2 min walk test (2MWT) was changed from 30 meters to 15.2 meters.
  - The waiting time between some tests were a bit longer (~10 min.) than planned due to other patients' rehabilitation practice in the health centre. Each testing session took roughly 90-100 minutes to conduct.
  - Due to a changed recruitment strategy (more people were screening for eligibility due to task shifting), several citizens were missed and therefore not asked to participate in the study. Further participants were hesitant to participate in the study due to COVID-19. Therefore, the result was a more extended recruitment period than initially described.

References

1. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.
2. Teljigovic S, Sogaard K, Sandal LF, Dalager T, Nielsen NO, Sjogaard G, et al. Individualised physical exercise training and enhanced protein intake in older citizens during municipality-based rehabilitation: protocol for a randomised controlled trial. BMJ Open. 2020;10(11):e041605.
3. Hunsaker FG, A. D, Cioffi M. The American Academy of Orthopaedix Surgeons Outcomes Instruments Normative Values From the General population. The Journal of Bone and Joint Surgery. 2002.
4. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice. 3 ed: Pearson/Prentice Hall; 2015. 892 p.
5. Cortina JM. What Is Coefficient Alpha? AN Examination of Theory and Applications. Journal of Applied Psychology. 1993;78:98-104.
6. Steiber N. Strong or Weak Handgrip? Normative Reference Values for the German Population across the Life Course Stratified by Sex, Age, and Body Height. PLoS One. 2016;11(10):1-14.
7. Abe T, Loenneke JP. Handgrip strength dominance is associated with difference in forearm muscle size. J Phys Ther Sci. 2015;27(7):2147-9.
8. Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. J Bone Joint Surg Am. 1999;81(9):1245-60.
9. Ponzer S, Skoog A, Bergstrom G. The Short Musculoskeletal Function Assessment Questionnaire (SMFA): cross-cultural adaptation, validity, reliability and responsiveness of the Swedish SMFA (SMFA-Swe). Acta Orthop Scand. 2003;74(6):756-63.
10. Reininga IH, el Moumni M, Bulstra SK, Olthof MG, Wendt KW, Stevens M. Cross-cultural adaptation of the Dutch Short Musculoskeletal Function Assessment questionnaire (SMFA-NL): internal consistency, validity, repeatability and responsiveness. Injury. 2012;43(6):726-33.
11. Bülow K, Christiansen T, Jørgensen ADB, Teljigovic S, editors. Hospitalized Geriatric Patients: A Descriptive Study. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; 2018: WCO-IOF-ESCEO.
12. Ekstrand E, Lexell J, Brogardh C. Grip strength is a representative measure of muscle weakness in the upper extremity after stroke. Top Stroke Rehabil. 2016;23(6):400-5.
13. Scoring instructions for Short Musculoskeletal Function Assessment (SMFA): University of Minnesota; 2021 [Available from: https://med.umn.edu/ortho/research/project-resources.