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Title: Changes in the severity of frailty among older adults after 12 months of supervised home-based physical exercise – A randomized clinical trial

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Brief summary: The RCT showed differences between the exercise and usual care groups in shifts between frailty states during a year as the severity of frailty was more often alleviated in the exercise group.

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ABSTRACT

Objective: To investigate the effects of 12 months of physiotherapist-supervised, home-based physical exercise on the severity of frailty and on the prevalence of the five frailty phenotype criteria, using secondary analyses.

Design: Randomized clinical trial, with 1:1 allocation into 12-month home-based physical exercise, or usual care. The multicomponent exercise sessions (60 minutes) were supervised by physiotherapist and included strength, balance, functional, and flexibility exercises twice a week at participants´ homes.

Setting and Participants: Home-dwelling older adults aged 65+ who were frail (meeting 3–5 criteria) or pre-frail (1–2 criteria) according to frailty phenotype criteria.

Methods: The severity of frailty (non-frail, pre-frail, frail) was assessed using frailty phenotype criteria, and the prevalence of each frailty criterion (weight loss, low physical activity, exhaustion, weakness, and slowness) were assessed at baseline and at 12 months.

Results: Two hundred ninety-nine persons were included in the analyses, of whom 184 were pre-frail and 115 were frail at baseline. Their mean age was 82.5 (SD 6.3) years, and 75% were women. There was a significant difference between the exercise and usual care groups' transitions to different frailty states from baseline to 12 months among those who at baseline were pre-frail ($p=0.032$) and frail ($p=0.009$). At 12 months, the mean number of frailty criteria had decreased in the exercise group (-0.27, 95% CI: -0.47 to -0.08) and remained unchanged in the usual care group (0.01, -0.16 to 0.18; $p=0.042$). The prevalence of the exhaustion ($p=0.009$) and the low physical activity ($p<0.001$) criteria were lower at 12 months in the exercise group than in the usual care group.

Conclusions and Implications: The severity of frailty can be reduced through 12-month supervised home-based exercise training. Exercise should be included in the care of older adults with signs of frailty.

INTRODUCTION

Frailty is a medical syndrome that occurs among older adults, more commonly among women than men.[1,2] A person with frailty has reduced physiological reserves which leads to vulnerability to external stressors[3] and causes a decline in functional capacity.[4] Frailty is a dynamic state that can fluctuate over time[5–8] but is more likely to deteriorate.[5, 9] The prevalence of frailty increases with age; among people over 50, the prevalence is around 12%[10] and of people over 80, almost one third might be frail.[2] People with frailty are at a higher risk of hospitalization,[11] longer hospital stays,[12] higher health care costs,[13] institutionalization,[14] and mortality.[5, 15]

Yet, frailty is not assessed routinely in primary or secondary health care.[16] There is no universal consensus or golden standard for how frailty should be assessed,[17] nor for how frailty should be prevented or managed.[2] The concepts most often used to define frailty are phenotypic physical frailty[18] and deficit accumulative frailty.[19] In physical frailty, frailty is seen as dysregulation of the stress-response, metabolism, and musculoskeletal systems.[20] The physical frailty phenotype consists of five criteria: weight loss, exhaustion, low physical activity, slowness, and weakness.[18] A person is classified as frail if they fulfill three or more criteria and pre-frail if they meet one or two.[18] In the deficit accumulative frailty, frailty is seen as sum of different health deficits such as symptoms, signs, disabilities, and diseases, and an index is calculated on the basis of whether a person has them or not.[21]

Sedentary behavior is associated with more severe frailty[22] and physical activity has been promising to reduce[23] and prevent[24] progression of frailty. Physical activity affects multiple physiological systems, and therefore might be the best option for prevention and treatment of physical frailty. [20] Multicomponent physical exercise with resistance training is one recommended treatment option,[25] but there is still scarcity of evidence on supervised home-based exercise programs. Other things to consider on frailty treatment are proper nutrition, addressing polypharmacy, and tackling probable causes of exhaustion (e.g., depression, anemia).[25]

The aim of these secondary analyses of the randomized controlled trial was to investigate the effects of a 12-month, physiotherapist-supervised, physical exercise program held twice a week at home on the severity of frailty of older adults with pre-frailty or frailty, and on the prevalence of the five phenotype criteria of physical frailty.

METHODS

Here we report the results of the secondary analyses of the randomized controlled trial with 1:1 allocation to the home-based physical exercise and the usual care groups. In November 2014, the study was approved by the coordinating ethics committee, and was registered to ClinicalTrials.gov (NCT02305433) in December 2014. The study protocol,[26] the results on the primary outcome days lived at home,[27] and on the secondary outcomes of utilization of social and health care, cost-effectiveness, quality of life,[27] and functioning[28] have been published earlier.

Participants

We recruited 300 home-dwelling older adults with signs of frailty from one region (population 131,000), in Finland between December 2014 and August 2016. Persons were recruited via advertisements in the local newspapers and by homecare personnel. Preliminary eligibility was evaluated using the FRAIL questionnaire. [29,30] It contains five questions on Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, and has scores of 0 or 1 and the total score ranges from 0 to 5.[29,30] A potential participant who scored at least one advanced to the next phase of recruitment.

Next, a research nurse evaluated eligibility during a home visit. The person had to meet all the inclusion criteria: age of ≥65 years, living at home, at least one of the physical frailty phenotype criteria,[18] a Mini-Mental State Examination (MMSE)[31] score of ≥17, able to walk indoors (walking aid allowed), and able to communicate in Finnish. Exclusion criteria were living in 24/7 care, problems with alcohol/drug abuse, severe problems with hearing/eyesight, a severe illness which is a contraindication for physical exercise (e.g., cardiovascular, neurological, or pulmonary disease) or a terminal disease (e.g., cancer). All the eligible and willing participants signed their written informed consent.

Intervention

The participants in the exercise group participated in one-hour physiotherapist-supervised physical exercise sessions at their homes, twice a week, for 12 months. The physiotherapists tailored the training to match individual participants' health and fitness status. The exercise sessions consisted of warm-up, strength, balance, functional and flexibility exercises. Training intensity was evaluated at the end of each session using Borg´s Ratings of Perceived Exertion (RPE) scale.[32] Target intensity was from moderate (12) to vigorous (17), and the intensity of the next session was modified accordingly. Strength training was divided into approximately eight-week periods of endurance, strength, and power training. To enable

progression, proper training resistance was ensured with multiple-repetition maximum tests, and the numbers of sets and repetitions were altered during the year according to the strength cycle and targeted intensity.

Strength training mainly focused on the lower limbs. Exercises were based on the Otago exercise program,[33] and included knee extension and flexion, hip abduction, and ankle plantarflexion (up on toes) and dorsiflexion (back on heels). Resistance was added with ankle weights and weight vests. In addition, participants performed upper body exercises with dumbbells and kettlebells, and sessions included functional exercises such as chair rises, climbing stairs or hanging laundry. The physiotherapists gave brief guidance on proper nutrition and encouraged the participants to also be physically active outside the supervised exercise sessions. A more detailed description of the exercise program can be found elsewhere.[26,28]

The usual care group continued to live their lives as usual. Both groups received any health or social care they needed during the year in accordance with the district's policies, including rehabilitation (e.g., physical, and occupational therapy).

Outcomes

The severity of frailty was assessed using a slightly modified version of Fried's frailty phenotype criteria.[18] These five criteria were weight loss, low physical activity, exhaustion, weakness, and slowness. The person's severity of frailty was classified according to the number of criteria met (0, non-frail; 1–2, pre-frail; and 3–5, frail). A research physiotherapist or a research nurse assessed the criteria at the participant's home at baseline and at 12 months. The assessors were not blinded for the allocation, but they did not participate in the implementation of the exercise intervention.

Weight was measured using an Omron HN289 scale (Japan). The frailty criterion of weight loss was met if the participants had unintentionally lost over 5% of their weight during the previous year. At baseline, the previous year´s weight was elicited from the participant and checked in electronic medical records, if available.

Low physical activity criterion was assessed by asking "How often do you do some physical activities such as walking, calisthenics, dancing etc.?" If the person was physically active less than once a week, 30 minutes at a time, they met the modified low physical exercise criterion. The modified criterion for low physical activity was based on a validated physical activity question from the FROP-Com (Falls Risk for Older People in the community) questionnaire.[34]

The exhaustion criterion included two questions from the Center of Epidemiology Studies Depression scale (CES-D):[35] "How often during the past week did you feel, that a) you could not get going? and b) everything you did was an effort?" The criterion was met if the person answered "most of the time" or "almost all the time" to either of the questions.

The slowness criterion was assessed by the time taken to walk four meters at the participant's usual pace from a standing start. If 4.0 m was impossible at the participant´s home, 2.44 m was used instead. Walking aids (e.g., cane, rollator) were allowed. The person had two attempts and the better result was used. The lowest fourth of the Short Physical Performance Battery (SPPB),[36] was used as the cutoff to enable validated and comparable times for both 4.0 and 2.44 meters. The person met the modified slowness criteria if they walked slower than 0.46 m/s (walking time >8.7 sec for 4 m and >5.2 sec for 2.44 m).

The weakness criterion was determined by handgrip strength, measured using the Saehan dynamometer (Sh5001, Masan, South Korea). The measurement was taken in a seated position, with the elbow unsupported at a 90-degree angle next to the body, and the wrist in a

neutral position. The best value of three attempts with the dominant hand was used. The cut-off values were defined by body mass index (BMI) and sex.[18] Cutoffs for women were ≤17 kg (BMI ≤26.0); ≤18 kg (BMI 26.1-29.0); ≤21 kg (BMI >29.0), and for men ≤29 kg (BMI ≤24.0); ≤30 kg (BMI 24.1-28.0); ≤32 kg (BMI >28.0). As background information, a Charlson comorbidity index[37] (CCI) was calculated on the basis of medical record information, and alcohol consumption with AUDIT-C-questionnaire[38], smoking habits and nutrition with Mini Nutritional Assessments[39] (MNA) were queried.

Allocation

After the baseline assessments, the participants were randomized without stratification into a home-based physiotherapist-supervised physical exercise intervention group (n=150) and a usual care group (n=150). The computer-generated, random sequence allocation program included varying block size from 2 to 10 and was created by a statistician who did not participate in either the conduction or analyses of this trial. One person in the research group who had not met the participant used the randomization program and telephoned them of their allocation result.

Statistical analysis

The sample size was calculated according to the primary outcome of days lived at home over 24 months.[27] In brief, to detect a difference (α (alpha) 0.05, β (power) 80%) of the hypothesized 180 (SD 431) days between the physical exercise and usual care groups, a sample size of 91 people was needed in each group (simulation-based effect size was 0.40). To allow for discontinuation (estimated as 15%) and death (20%) of participants over 12 months, our targeted sample size was 300 participants.

All analyses were performed according to the intent-to-treat principle. Descriptive statistics of the participants are presented as means with standard deviations (SD), or as frequencies with percentages (%). The relationship between the randomization groups and frailty status at baseline was evaluated using a two-way analysis of variance (ANOVA) and logistic model. Models include main effects of randomization group and frailty status and their interaction.

Changes (transition frequencies) in the states of severity of frailty (defined as non-frail, pre-frail, frail, dead) were analyzed over 12 months using conditional fixed-effects multinomial logit models. Changes in single frailty criteria were analyzed using the Generalized Estimating Equation (GEE). If the assumptions were violated, a bootstrap-type or permutation test was used. Hommel's adjustment was applied to correct the levels of significance for multiple testing, if appropriate. The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. The Stata 17.0, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

RESULTS

There were 299 participants (Figure 1) in the analyses, 150 in the exercise group and 149 in the usual care group, as one participant withdrew from the trial after allocation to the usual care group and refused to allow the use of her data. At baseline, the mean age was 82.5 (SD 6.3, range 65 to 98) years, 75% of the participants were women, and 184 participants were classified as pre-frail, and 115 as frail (Table 1).

Among those who were pre-frail at baseline, in the exercise group, the status changed to non-frail in 15 participants, to frail in 7, and 5 died. In the usual care group, the status changed to non-frail in 8 participants, to frail 20, and 7 died (Figure 2A). The transition frequencies from

185 the pre-frailty status were significantly different (p=0.032) in the exercise and the usual care
186 groups over 12 months.

187 Among the participants who were frail at baseline, in the exercise group 35 became pre-frail
188 and 3 non-frail. In the usual care group, 17 became pre-frail, 1 non-frail and 3 died. The
189 transition frequencies from the frailty status over the12 months were significantly different
190 (p=0.009) in the exercise and the usual care groups (Figure 2B).

191 The mean number of frailty criteria met at baseline was 2.2 (SD 1.1) in the exercise group
192 and 2.2 (1.0) in the usual care group (p=0.82) (Table 1). After 12 months, the change was -
193 0.27, (95% CI -0.47 to -0.08) in the exercise and 0.01, (95% CI -0.16 to 0.18) in the usual
194 care group and the difference was significant (p=0.042). As regards the single frailty criterion
195 at baseline, the three most often met were exhaustion (62%), weakness (60%), and low
196 physical activity (54%) (Table 1). After 12 months, one third of the participants in the
197 exercise group and half of those in the usual care group met the exhaustion criterion
198 (p=0.009) (Figure 3). The prevalence of the low physical activity criterion decreased to 14%
199 in the exercise group, whereas it remained unchanged in the usual care group (p<0.001).
200 There were no differences between the groups in weight loss, slowness, or weakness criteria
201 at 12 months, and no changes in the prevalence within groups (Figure 3).

202 The median number of completed exercise sessions was 96 (IQR 89, 99). The majority of
203 participants reported mild and transient muscle soreness (58%) or mild joint pain (71%) after
204 some exercise sessions. One fall led to mild injury. Eighteen participants took nitroglycerin
205 during the session. On five occasion the participants needed acute medical care (unrelated to
206 exercise) at the arrival of the physiotherapist.

207 **DISCUSSION**

The 12-month home-based, physiotherapist-supervised, physical exercise program slowed down or reversed the progression of frailty in older persons with at least one of the frailty phenotype criteria at baseline. With regard to the single frailty criteria, physical exercise most prominently decreased the prevalence of low physical activity and of exhaustion in comparison to usual care.

Our 12-month exercise intervention slightly reduced the mean number of frailty criteria met. Compared to the usual care group, more participants in the exercise group maintained their pre-frail state or reversed to non-frailty, and fewer participants advanced to frailty. Earlier studies have shown that the severity of frailty can naturally fluctuate over time, but the transition is more likely to be towards worse than better.[5–7] A study using the frailty index found that natural fluctuations increased with age and frailty levels among community-dwelling older adults.[40] Previously, six months of supervised, center-based physical exercise five times a week,[41] and a 12-month program with individually tailored supervised and unsupervised physical exercise, nutrition counseling and social interaction sessions[42] have lowered the severity of physical frailty among people who were already frail. The severity of physical frailty also diminished among sedentary older adults after a 12-month physical activity intervention in comparison to participants in a health education group.[43] Among sedentary older adults, an intervention using center- and home-based physical activity did not reduce the overall risk of developing frailty, measured using the SOF frailty index, over 24 months, in comparison to a health education group.[44]

In terms of the single frailty phenotype criterion, participation in our 12-month supervised home-based exercise significantly lowered the prevalence of the low physical activity and the exhaustion criterion. Other studies using 12-month exercise interventions have also reported lower prevalence of the low physical activity criterion, but not of the exhaustion criterion

among people with frailty[42] and among sedentary older adults.[43] In general, pre-frail and frail people have fewer social networks than the non-frail,[45] and loneliness and social isolation increase the risk of more severe frailty.[46,47] Many of our participants lived alone, and the physiotherapist's visits provided regular social contact for them. Our participants' physical performance[28] also improved after the 12-month intervention, which may reduce the feeling of exhaustion.

Over 12 months, there were no differences between the study groups in the prevalence's of slowness, weakness, or weight loss criteria. In contrast to our findings concerning the slowness criterion, an earlier study[42] found a significant difference between their usual care and the exercise groups' walking speeds after 12 months in favor of the exercise group. We used a slightly modified slowness criterion to enable validated, comparable cutoff values at distances of 2.44 and 4 m,[36] which enabled the option of shorter walking distance in small homes. This change may have made our participants less frail than they would have been if the original frailty phenotype walking speed's cutoff[18] had been used. There was no difference between the grip strength of our groups at 12 months. An earlier study found that 24-week resistance exercise had no effect on grip strength among pre-frail and frail older adults, although it did increase physical performance and maximum leg strength.[48] With regard to the weight loss criterion, other randomized physical exercise intervention studies have also detected no change in the prevalence.[41-44]

One of the strengths of our trial was that it followed a rigorous randomized design, and both groups had good compliance. We were able to recruit the targeted amount of physically pre-frail and frail people,[49] which enabled us to analyze the change in the severity of frailty as planned. Our participants had varied socioeconomical backgrounds and were from both cities and rural areas. In addition, all measurements, assessments, and the exercise intervention

were performed at the participants' homes and were free of charge to our participants, which made the program more accessible.

As for limitations, frailty was not our primary outcome, and we used a slightly modified version of the frailty phenotype criteria[18] to assess frailty. Phenotype criteria are one of the most commonly used tools in research to assess physical frailty,[18] and modifications to the criteria are not uncommon.[50] However, this may influence the comparability of studies. In addition, we only assessed the severity of frailty at baseline and at 12 months and did not follow the participants' severity of frailty further. A third limitation was that neither participants nor assessors were blinded for the allocation.

CONCLUSIONS AND IMPLICATION

Our findings support the concept that frailty is a reversible condition, and the home-based physiotherapist-supervised 12-month physical exercise regimen seemed to slow down and reverse frailty progression. Our exercise program was most effective in reducing exhaustion and low physical activity. Exercise should be included as part of the care of older adults with signs of frailty.

Conflicts of interest disclosure: Authors declare no conflicts of interest.

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Table and Figure titles and legends

Table 1. Baseline characteristics in usual care and physical exercise groups, and in subgroups of pre-frail and frail. Means (SD) or frequencies (%).

Figure 1. Flowchart of study.

Figure 2. A) Status at 12 months for those who were pre-frail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from pre-frailty to the status of non-frail, pre-frail, frail, and death; mean with 95% confidence interval whiskers. Statistical significance of transition frequencies between the randomization groups p=0.032. B) Status at 12 months for those who were frail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from frailty to the status of non-frail, pre-frail, frail, and death; mean with 95% confidence interval whiskers. Statistical significance of transition frequencies between the randomization groups p=0.009.

Figure 3. Prevalence (frequency percentages, %) of the participants meeting the five frailty phenotype criteria (weight loss, low physical activity, exhaustion, weakness, and slowness) at baseline and at 12 months, by randomizations groups (usual care and physical exercise) Means with 95% confidence interval whiskers. Hommel's multiple comparison procedure was used to correct significance; only statistically significant p-values are presented.

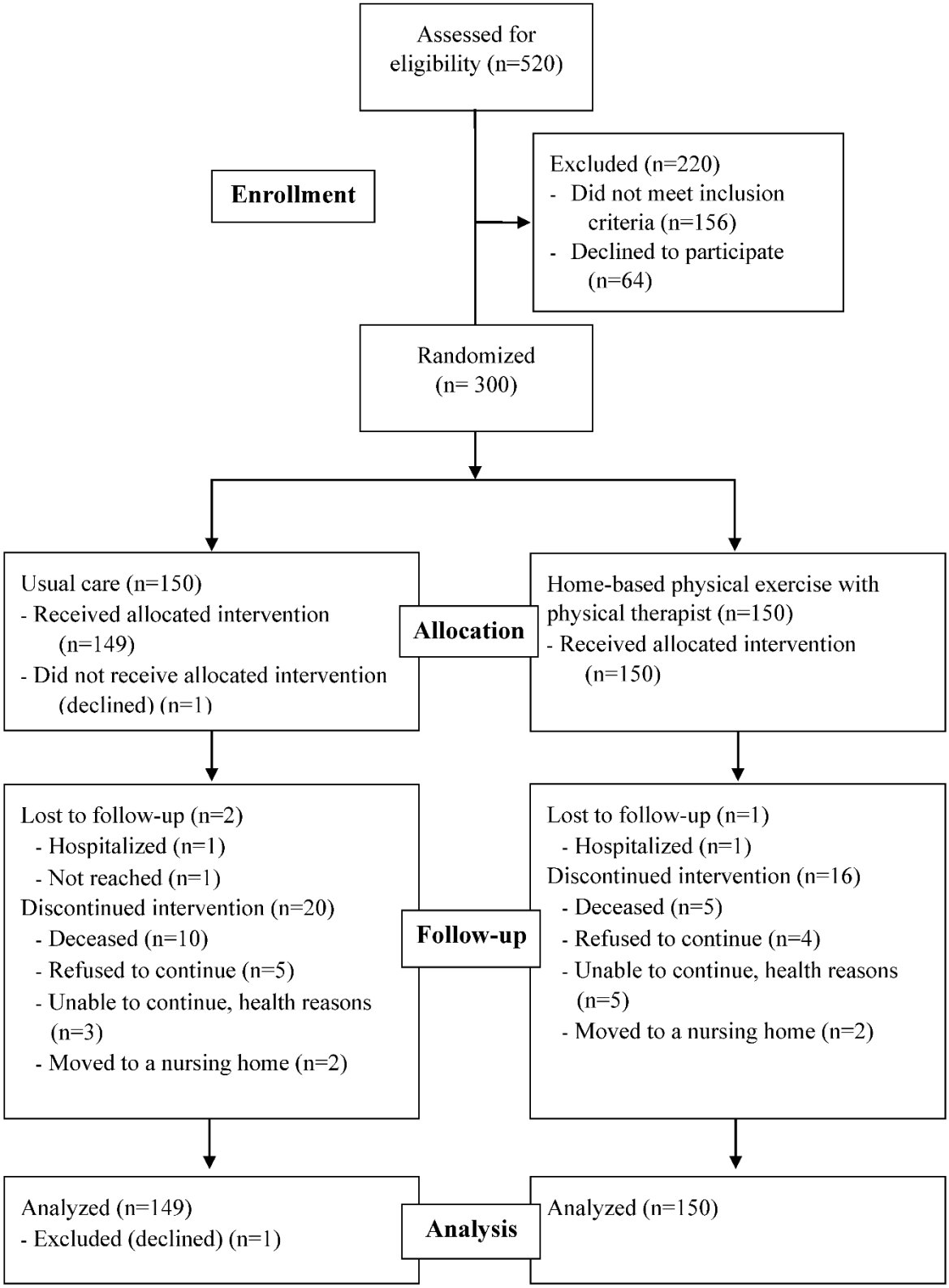
451 **Table 1.** Baseline characteristics in usual care and physical exercise groups, and in
452 subgroups of pre-frail and frail. Means (SD) or frequencies (%).

453

	Usual care	Physical exercise	Usual care		Physical exercise		p-values[†]		
	All	All	Pre-frail[*]	Frail[*]	Pre-frail[*]	Frail[*]	Main effects		Interaction
Characteristics	n=149	n=150	n=92	n=57	n=92	n=58	Group	Frailty	
Women, n (%)	110 (74)	114 (76)	66 (72)	44 (77)	68 (74)	46 (79)	0.68	0.29	0.98
Age, years, mean (SD)	83 (6)	82 (6)	82 (7)	84 (5)	82 (6)	82 (7)	0.31	0.32	0.29
BMI[‡], mean (SD)	28.6 (6.1)	28.4 (5.5)	28.7 (6.2)	28.5 (5.8)	28.0 (5.8)	29.2 (4.9)	0.98	0.46	0.28
Walking m/s, mean (SD)	0.64(0.24)	0.62 (0.24)	0.73 (0.21)	0.50 (0.22)	0.71 (0.22)	0.49 (0.21)	0.58	<0.001	0.84
Handgrip strength, kg,									
Women, mean (SD)	17.8 (5.7)	17.1 (6.5)	18.6 (6.1)	16.6 (4.9)	18.7 (5.3)	14.8 (7.4)	0.51	<0.001	0.90
Men, mean (SD)	30.0 (7.5)	28.5 (7.5)	32.8 (6.6)	24.5 (6.3)	29.1 (8.4)	27.3 (5.3)	0.82	0.010	0.028
Living alone, n (%)	86 (58)	88 (59)	43 (47)	43 (75)	54 (59)	34 (58)	0.56	0.013	0.013
MMSE[§], mean (SD)	24.6 (3.2)	24.2 (3.1)	24.9 (3.3)	24.0 (2.9)	24.8 (3.0)	23.4 (3.0)	0.32	0.001	0.58
CCI[‖], mean (SD)	2.0 (1.7)	2.0 (1.7)	1.8 (1.6)	2.3 (1.8)	1.9 (1.4)	2.1 (1.9)	0.67	0.090	0.41
Current smoking, n (%)	3 (2)	9 (6)	2 (2)	1 (2)	5 (5)	4 (7)	0.094	0.98	0.74
AUDIT-C[**], mean (SD)	1.0 (1.3)	11 (1.1)	1.1 (1.3)	1.0 (1.5)	0.9 (1.1)	1.3 (1.3)	0.51	0.33	0.13
MNA[††], mean (SD)	22.7 (3.4)	23.3 (3.1)	23.7 (2.7)	21.4 (3.9)	23.8 (3.1)	22.6 (2.9)	0.069	<0.001	0.13
Frailty criteria, n (%)									
Weight loss	27 (18)	26 (17)	7 (8)	20 (35)	9 (10)	17 (29)	0.98	<0.001	0.41
Low physical activity	83 (56)	77 (51)	30 (33)	53 (91)	32 (35)	45 (76)	0.10	<0.001	0.075

Exhaustion	96 (64)	90 (60)	56 (62)	40 (69)	37 (41)	53 (90)	0.28	<0.001	<0.001
Slowness	33 (22)	48 (32)	4 (4)	29 (50)	11 (12)	37 (63)	0.020	<0.001	0.30
Weakness	85 (57)	94 (63)	37 (41)	48 (83)	49 (54)	45 (76)	0.68	<0.001	0.25
Frailty score‡‡, n (%)							0.69	-	-
1	48 (32)	44 (29)	48 (52)	-	44 (48)	-			
2	44 (30)	48 (32)	44 (48)	-	48 (52)	-			
3	42 (28)	40 (27)	-	42 (74)	-	40 (69)			
4	13 (9)	13 (9)	-	13 (23)	-	13 (22)			
5	2 (1)	5 (3)	-	2 (3)	-	5 (9)			

Note. * Participants were classified as pre-frail if they met one or two of the frailty criteria and frail if they met three or more; †A two-way analysis of variance (ANOVA) and logistic model including main effects of randomization groups and frailty status and their interaction. ‡ BMI, Body Mass Index (kg/m^2); §MMSE, Mini-Mental State Examination[31]; ‖CCI, Charlson Comorbidity Index[37]; ** AUDIT-C, Alcohol Use Disorders Identification Test[38; ††]MNA, Mini Nutritional Assessment[39]; ‡‡Number of frailty criteria fulfilled



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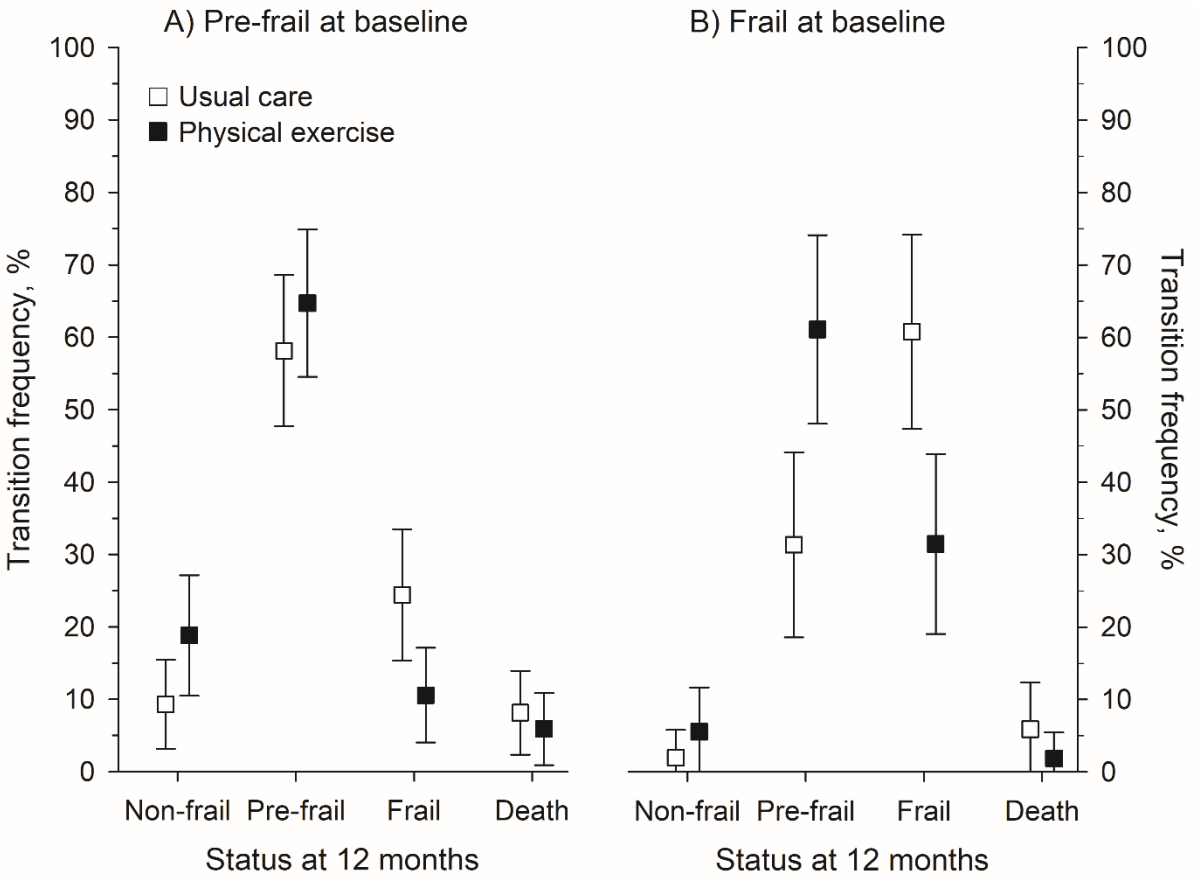
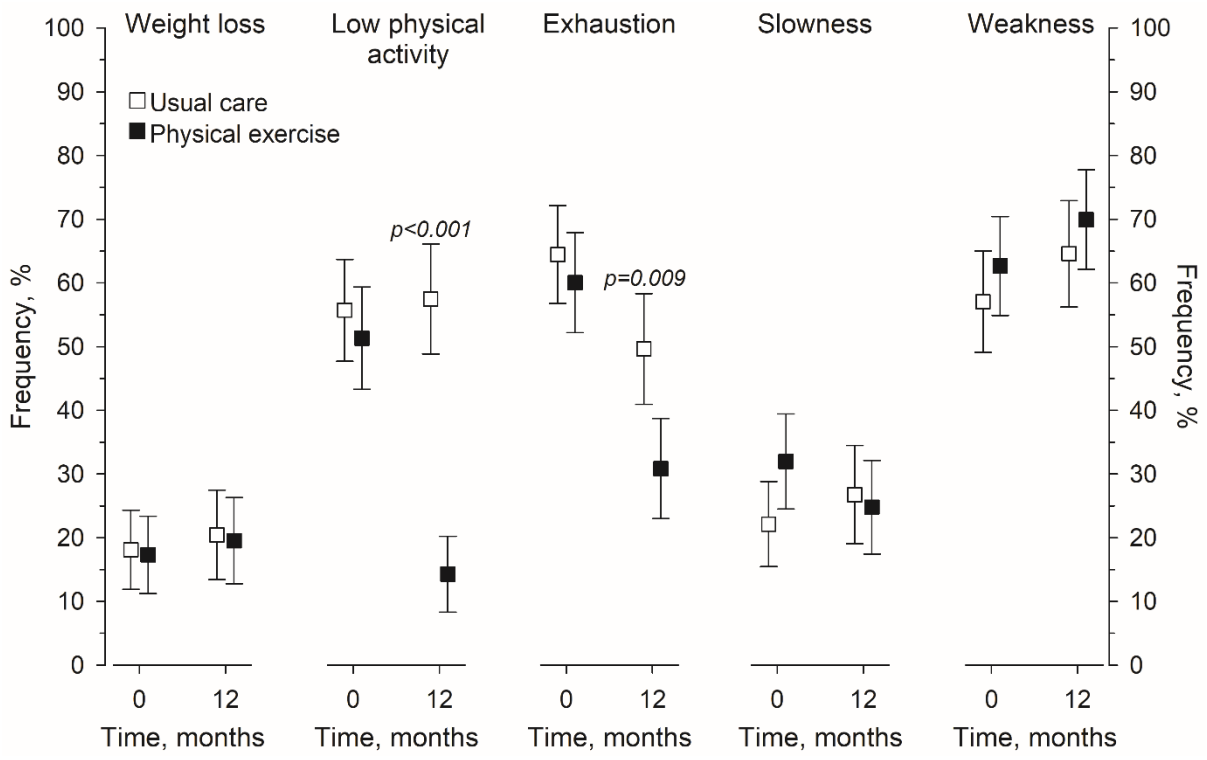


Figure 2. A) Status at 12 months for those who were pre-frail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from pre-frailty to the status of non-frail, pre-frail, frail, and death; mean with 95% confidence interval whiskers. Statistical significance of transition frequencies between the randomization groups p=0.032. B) Status at 12 months for those who were frail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from frailty to the status of non-frail, pre-frail, frail, and death; mean with 95% confidence interval whiskers. Statistical significance of transition frequencies between the randomization groups p=0.009.



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