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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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## 1 ABSTRACT

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

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

9 **Setting and Participants:** Home-dwelling older adults aged 65+ who were frail (meeting 3–  
10 5 criteria) or pre-frail (1–2 criteria) according to frailty phenotype criteria.

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

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

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

## 26 INTRODUCTION

27 Frailty is a medical syndrome that occurs among older adults, more commonly among  
28 women than men.<sup>1,2</sup> A person with frailty has reduced physiological reserves which leads to  
29 vulnerability to external stressors<sup>3</sup> and causes a decline in functional capacity.<sup>4</sup> Frailty is a  
30 dynamic state that can fluctuate over time<sup>5-8</sup> but is more likely to deteriorate.<sup>5,9</sup> The  
31 prevalence of frailty increases with age; among people over 50, the prevalence is around  
32 12%<sup>10</sup> and of people over 80, almost one third might be frail.<sup>2</sup> People with frailty are at a  
33 higher risk of hospitalization,<sup>11</sup> longer hospital stays,<sup>12</sup> higher health care costs,<sup>13</sup>  
34 institutionalization,<sup>14</sup> and mortality.<sup>5,15</sup>

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

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

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

57

## 58 **METHODS**

59 Here we report the results of the secondary analyses of the randomized controlled trial with  
60 1:1 allocation to the home-based physical exercise and the usual care groups. In November  
61 2014, the study was approved by the coordinating ethics committee, and was registered to  
62 ClinicalTrials.gov (NCT02305433) in December 2014. The study protocol,<sup>26</sup> the results on  
63 the primary outcome days lived at home,<sup>27</sup> and on the secondary outcomes of utilization of  
64 social and health care, cost-effectiveness, quality of life,<sup>27</sup> and functioning<sup>28</sup> have been  
65 published earlier.

66

## 67 **Participants**

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

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

### 83 **Intervention**

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

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

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

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

107

## 108 **Outcomes**

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



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

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

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

130 The slowness criterion was assessed by the time taken to walk four meters at the participant's  
131 usual pace from a standing start. If 4.0 m was impossible at the participant's home, 2.44 m  
132 was used instead. Walking aids (e.g., cane, rollator) were allowed. The person had two  
133 attempts and the better result was used. The lowest fourth of the Short Physical Performance  
134 Battery (SPPB)<sup>36</sup> was used as the cutoff to enable validated and comparable times for both  
135 4.0 and 2.44 meters. The person met the modified slowness criteria if they walked slower  
136 than 0.46 m/s (walking time >8.7 sec for 4 m and >5.2 sec for 2.44 m).

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

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

### 147 **Allocation**

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

### 155 **Statistical analysis**

156 The sample size was calculated according to the primary outcome of days lived at home over  
157 24 months.<sup>27</sup> In brief, to detect a difference ( $\alpha$  (alpha) 0.05,  $\beta$  (power) 80%) of the  
158 hypothesized 180 (SD 431) days between the physical exercise and usual care groups, a  
159 sample size of 91 people was needed in each group (simulation-based effect size was 0.40).  
160 To allow for discontinuation (estimated as 15%) and death (20%) of participants over 12  
161 months, our targeted sample size was 300 participants.

162 All analyses were performed according to the intent-to-treat principle. Descriptive statistics  
163 of the participants are presented as means with standard deviations (SD), or as frequencies  
164 with percentages (%). The relationship between the randomization groups and frailty status at  
165 baseline was evaluated using a two-way analysis of variance (ANOVA) and logistic model.  
166 Models include main effects of randomization group and frailty status and their interaction.  
167 Changes (transition frequencies) in the states of severity of frailty (defined as non-frail, pre-  
168 frail, frail, dead) were analyzed over 12 months using conditional fixed-effects multinomial  
169 logit models. Changes in single frailty criteria were analyzed using the Generalized  
170 Estimating Equation (GEE). If the assumptions were violated, a bootstrap-type or  
171 permutation test was used. Hommel's adjustment was applied to correct the levels of  
172 significance for multiple testing, if appropriate. The normality of variables was evaluated  
173 graphically and using the Shapiro–Wilk W test. The Stata 17.0, StataCorp LP (College  
174 Station, TX, USA) statistical package was used for the analyses.

175

## 176 **RESULTS**

177 There were 299 participants (Figure 1) in the analyses, 150 in the exercise group and 149 in  
178 the usual care group, as one participant withdrew from the trial after allocation to the usual  
179 care group and refused to allow the use of her data. At baseline, the mean age was 82.5 (SD  
180 6.3, range 65 to 98) years, 75% of the participants were women, and 184 participants were  
181 classified as pre-frail, and 115 as frail (Table 1).

182 Among those who were pre-frail at baseline, in the exercise group, the status changed to non-  
183 frail in 15 participants, to frail in 7, and 5 died. In the usual care group, the status changed to  
184 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 the 12 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 occasions the participants needed acute medical care (unrelated to  
206 exercise) at the arrival of the physiotherapist.

207 **DISCUSSION**

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

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

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

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

238 Over 12 months, there were no differences between the study groups in the prevalence's of  
239 slowness, weakness, or weight loss criteria. In contrast to our findings concerning the  
240 slowness criterion, an earlier study<sup>42</sup> found a significant difference between their usual care  
241 and the exercise groups' walking speeds after 12 months in favor of the exercise group. We  
242 used a slightly modified slowness criterion to enable validated, comparable cutoff values at  
243 distances of 2.44 and 4 m,<sup>36</sup> which enabled the option of shorter walking distance in small  
244 homes. This change may have made our participants less frail than they would have been if  
245 the original frailty phenotype walking speed's cutoff<sup>18</sup> had been used. There was no  
246 difference between the grip strength of our groups at 12 months. An earlier study found that  
247 24-week resistance exercise had no effect on grip strength among pre-frail and frail older  
248 adults, although it did increase physical performance and maximum leg strength.<sup>48</sup> With  
249 regard to the weight loss criterion, other randomized physical exercise intervention studies  
250 have also detected no change in the prevalence.<sup>41-44</sup>

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

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

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

265

## 266 **CONCLUSIONS AND IMPLICATION**

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

272

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

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430 **Table and Figure titles and legends**

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

433 **Figure 1.** Flowchart of study.

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

443

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

450

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 (%).

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Characteristics	Usual care	Physical exercise	Usual care		Physical exercise		p-values <sup>†</sup>		
	All n=149	All n=150	Pre-frail* n=92	Frail* n=57	Pre-frail* n=92	Frail* n=58	Main effects Group p	Frailty y	Interaction
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 <sup>‡</sup> , 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 <sup>§</sup> , 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 <sup>  </sup> , 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 <sup>**</sup> , 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 <sup>††</sup> , 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

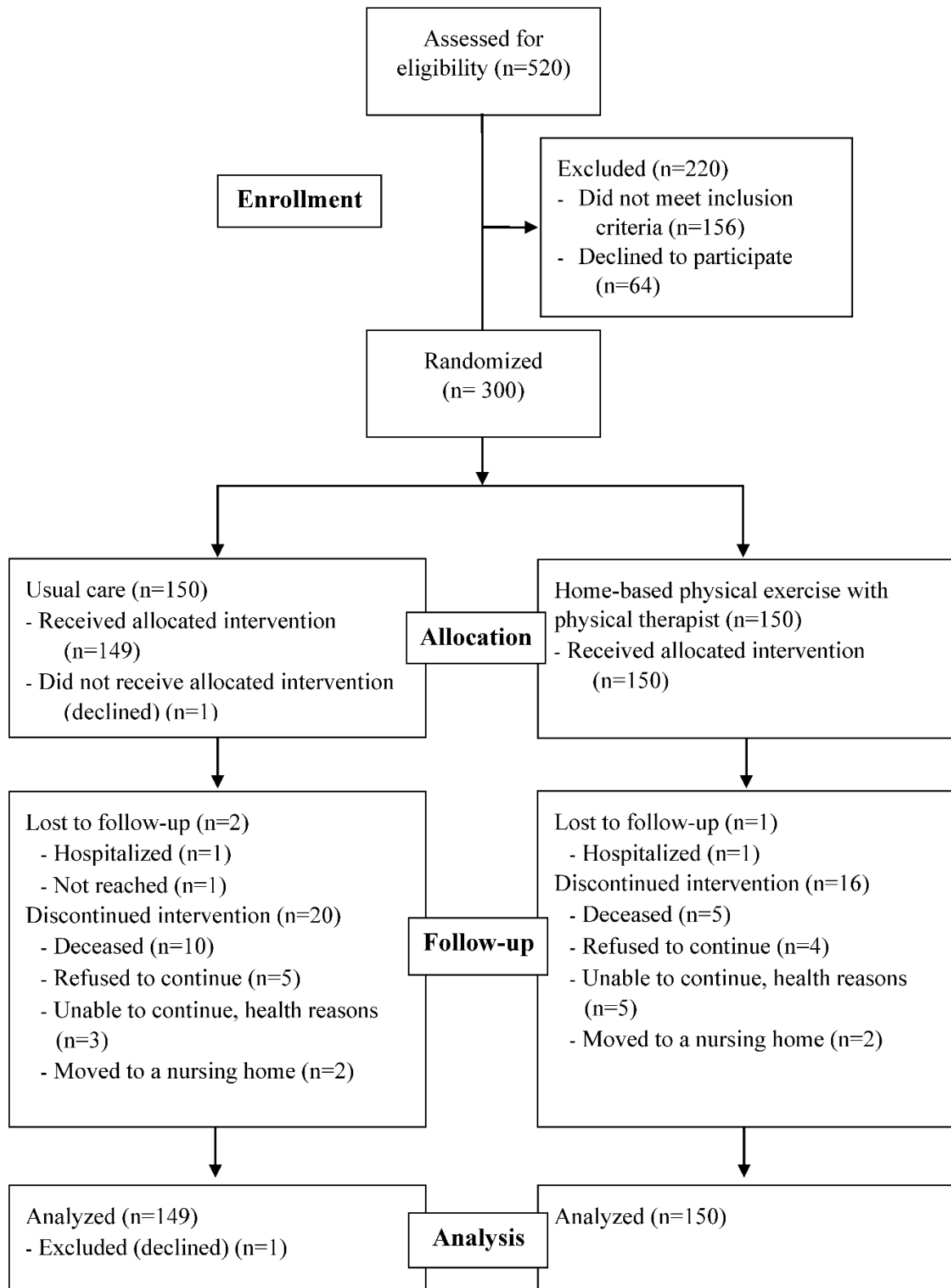


Exhaustion	96 (64)	90 (60)	56 (62)	40 (69)	37 (41)	53 (90)	0.28	<0.00 1	<0.001
Slowness	33 (22)	48 (32)	4 (4)	29 (50)	11 (12)	37 (63)	0.02	<0.00 1	0.30
Weakness	85 (57)	94 (63)	37 (41)	48 (83)	49 (54)	45 (76)	0.68	<0.00 1	0.25
Frailty score <sup>††</sup> , n (%)							0.69	-	-
1	48 (32)	44 (29)	48 (52)	-	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)			

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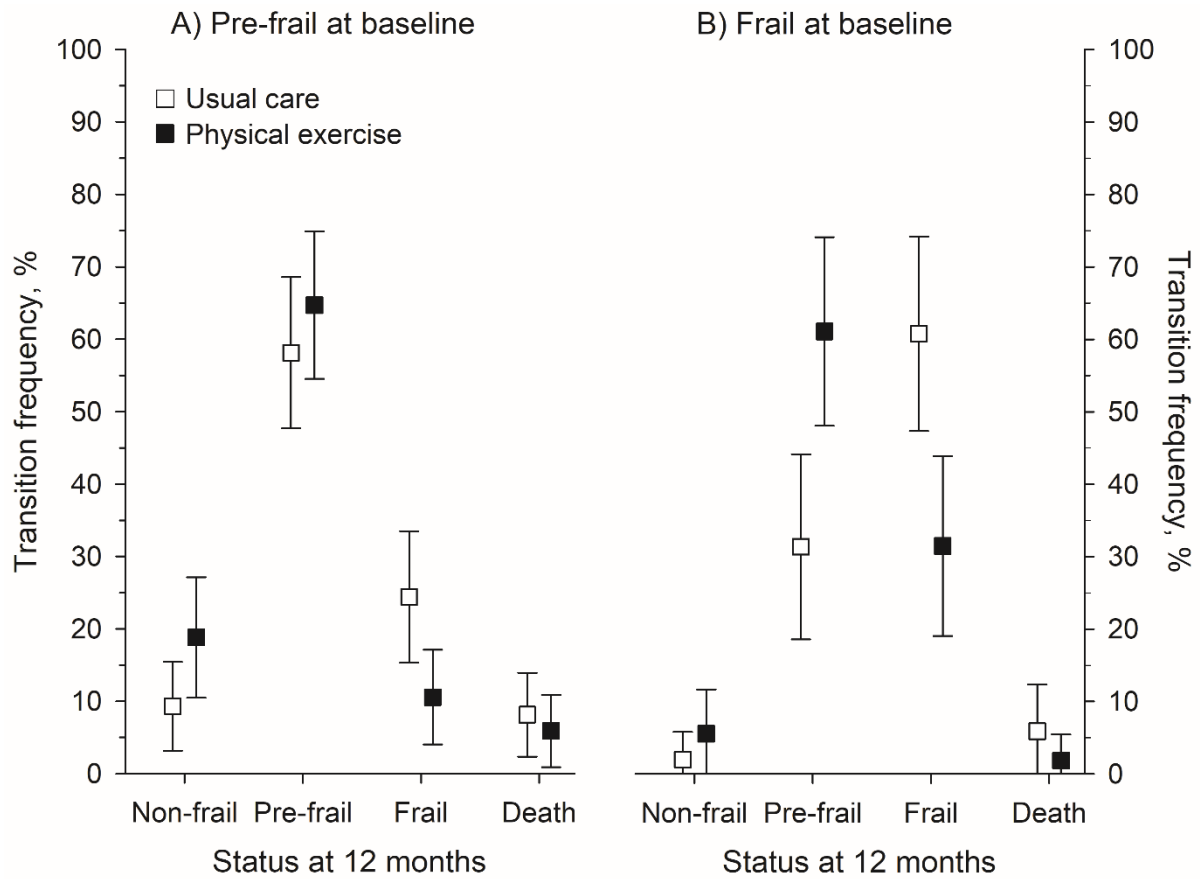


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**Figure 1.** Flowchart of study.

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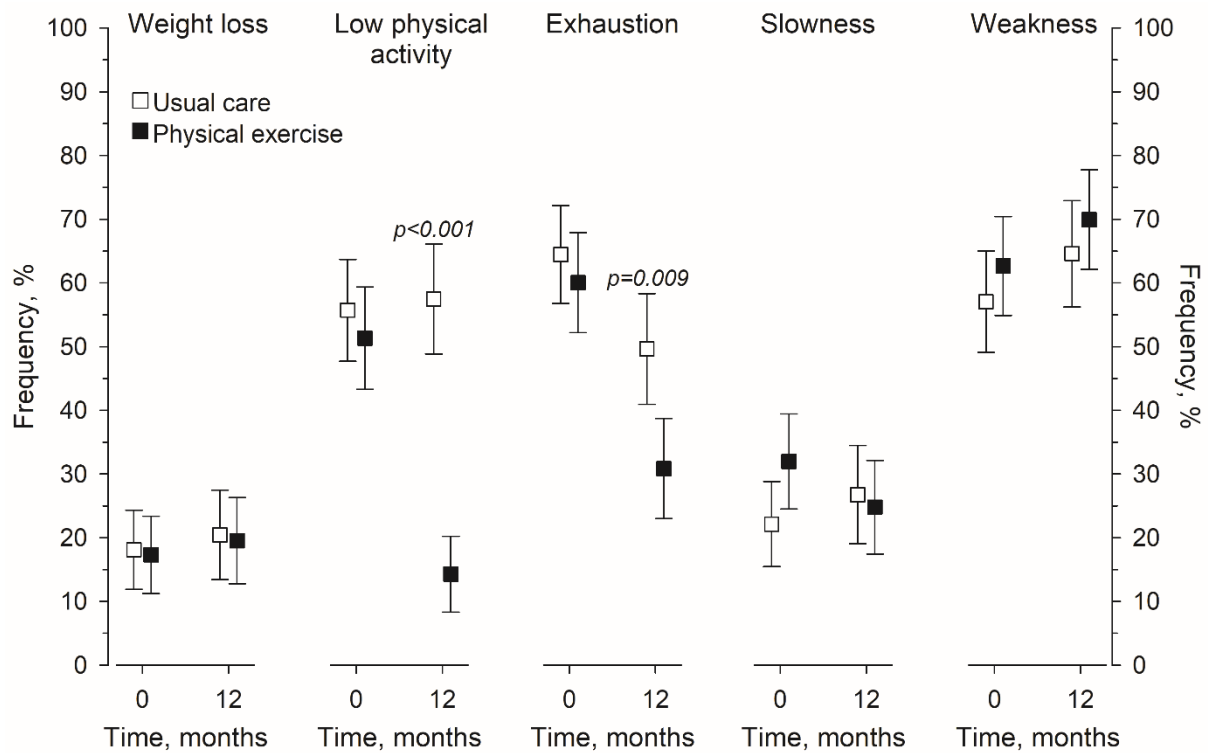
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**Figure 2.** A) Status at 12 months for those who were pre-frail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from pre-frailty to the status of non-frail, pre-frail, frail, and death; mean with 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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**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.