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Research paper

Severity of frailty and the outcome of exercise intervention among participants with Alzheimer disease: A sub-group analysis of a randomized controlled trial

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ABSTRACT

Introduction: To investigate how frailty status affects the outcome of exercise intervention among home-dwelling participants with Alzheimer disease (AD).
Methods: This is a sub-group analysis of a randomized controlled trial. In this trial, home-dwelling participants with AD received either home-based or group-based exercise twice a week for one year (n = 129); the control group received normal care (n = 65). Both the intervention and control group were subdivided into two groups according to modified Fried criteria: prefrail (0–1 criteria) and advanced frailty (2–5 criteria). The Functional Independence Measure (FIM) and number of falls per person-years served as outcome measures.
Results: Whereas there was no significant difference in FIM between the prefrail intervention (PRI) and control (PRC) groups at 3 or 6 months, the PRI group deteriorated significantly slower at 12 months (−6.6 [95% CI −8.6 to −4.5] for PRI and −11.1 [95% CI −13.9 to −8.3] for PRC; P = 0.010). Similarly, there was no significant difference between the advanced frailty intervention (AFI) and control (AFC) groups at 3 months, but the difference became significant at 6 months (−8.1 [95% CI −11.1 to −5.2] for AFI and −15.5 [95% CI −20.0 to −11.1] for AFC; P = 0.007) and at 12 months (−8.9 [95% CI −11.9 to −5.9] for AFI and −15.3 [95% CI −20.2 to −10.3] for AFC; P = 0.031). There was also a significant difference in the number of falls in favor of PRI and AFI groups compared to their respective control groups.
Conclusion: A long-term exercise intervention benefited people with AD regardless of their stage of frailty.
Trial registration: : ACTRN12608000037303.

1. Introduction

The term frailty is used to describe older people whose health has deteriorated, without being a direct consequence of one or multiple diseases [1]. Older people with frailty are vulnerable to multiple complications [1,2]. Researchers have proposed several definitions for frailty, but the Fried criteria [3] are the most frequently used [4]. Although Fried criteria based only on physical conditions have come under criticism for failing to take into consideration biological, psychological and social dimensions [5], limiting the definition to individual's physical dimension simplifies research and enables comparison of different studies [5].

Frailty is known to have poor prognosis [2], as it leads to disabilities, complications and increased risk of death [1–3,6,7]. The prevention and treatment of frailty has seen extensive research [8]. Several systematic reviews suggest that exercise benefits frail people by improving their balance, gait speed and functioning [9–11]. Most benefits derive from diverse, long-term

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and intense exercise training [11]. Diverse strength, balance and endurance training seems most effective in decreasing the number of falls and in improving gait and physical ability to function among physically frail older people [12]. Some researchers have suggested that exercise intervention may benefit prefrail people more than frail people [13]. However, a recent study found that frail participants benefited the most from physical activity intervention [14]. Other researchers have argued that physical activity intervention may even reduce frailty [14,15].

A number of studies have shown that frailty increases the risk for cognitive decline, and that cognitive impairments increase the risk for frailty [16]. Frailty and dementia share similar features: both conditions increase with aging and share the same etiological factors, such as smoking, low physical activity, obesity and depression [17]. Malnutrition and weight loss are common problems in both AD [18] and frailty [12]. The loss of lean mass leads to an increased risk for sarcopenia in AD [19], which is associated with frailty [20]. A decrease in muscle mass and strength predisposes older adults to both frailty and falls [3].

Although people with dementia seem to benefit from exercise interventions [21–23], to our knowledge, no intervention studies have explored how the frailty status of people with Alzheimer disease modifies the effectiveness of exercise. This study is a sub-group analysis of a randomized controlled trial, which investigated the costs and effects of an exercise intervention on participants with Alzheimer disease [23]. The aim of this study was to investigate how the frailty status of participants with Alzheimer disease modifies the outcome of an intense and long-term exercise intervention with respect to their physical functioning and falls.

2. Methods

The original randomized, controlled FINALEX study comprised two active intervention arms: home-based and group-based exercise intervention, both of which consisted of similar exercise components in approximately one-hour sessions held twice weekly for one year [23]. For this sub-analysis, we merged both exercise groups into one intervention group. Physiotherapists supervised both types of interventions. For the sub-group analysis, we subdivided both the control group and the intervention group into two groups according to their frailty status: a prefrail intervention group (PRI) and a prefrail control group (PRC) meeting 0–1 of the five Fried criteria [3], and an advanced frailty intervention group (AFI) and an advanced frailty control group (AFC) meeting 2–5 of the five Fried criteria.

2.1. Participants

In 2008, the Social Insurance Institution of Finland used its drug reimbursement register to recruit Alzheimer patients living with a spouse in the cities of Helsinki, Espoo or Vantaa ($n = 1264$). Altogether 497 persons expressed an interest in participating. Study nurses managed to contact 390 persons, 84 of which did not wish to participate and 96 did not fulfil the inclusion criteria, which were:

- speaking Finnish language;
- living with a spouse at home;
- living in Helsinki, Espoo or Vantaa;
- $\geq$ 65 years, retired;
- no diagnosed terminal disease or difficult hemiplegia;
- the ability to walk independently with or without a mobility aid.

All participants had to have at least one of the following signs of possible frailty: $\geq$ 1 falls during the previous 12 months, unintentional weight loss, or decreased walking speed. Therefore, some participants may have had only a fall as a sign of frailty, and so did not meet any of the modified Fried criteria. A total of 210 patients met our inclusion criteria and participated in the study.

The Ethics Committee of the Helsinki University Central Hospital approved the study, and all patients provided informed consent. Spouses provided informed consent for patients with reduced judgment capacity.

2.2. Clinical measures

We collected data on demographic factors (age, sex, education) at baseline. The Mini Nutritional Assessment (MNA) served to assess the participants' nutritional status [24], and their medical records served to confirm their medication and comorbidities; we then calculated the Charlson comorbidity index [25]. The Clinical Dementia Rating (CDR) scale [26] and the Mini Mental State Examination (MMSE) [27] served to evaluate cognitive status, and the Functional Independence Measure (FIM) [28] to evaluate physical functioning.

The participants in either intervention arms and the participants in the control group were divided into two groups according to their clinical stage of frailty as determined by the modified Fried criteria [3]. In this study, the five frailty criteria were:

- unintentional weight loss – the spouse was asked (yes/no);
- exhaustion – based on item retrieved from Cornell Scale for Depression in Dementia [29]: "Lack of energy: fatigues easily, unable to sustain activities";
- low physical activity – the question inquired whether the participant exercised in their leisure time (yes/no);
- slowness – based on the walking speed in the Short Physical Performance Battery test (SPPB) (< 0.85 m/s) [30];
- weakness – based on the grip strength in the SPPB test [30].

Patients meeting none or only one of the above criteria were classified into the prefrail groups (PRI and PRC), and patients meeting 2–5 criteria were classified into the advanced frailty groups (AFI and AFC).

We examined the effects of an exercise intervention on physical functioning during a one-year follow-up among Alzheimer patients with various stages of frailty in both groups (PRI vs. PRC and AFI vs. AFC) separately. We assessed the effects of the intervention as changes in FIM [28]. We assessed FIM values at baseline, 3, 6, and 12 months based on the caregiver's evaluation of the patient's performance at home. FIM assesses both physical (13 questions) and cognitive functioning (5 questions). Each item is evaluated on a 1- to 7-point scale (1 = the greatest need for help; 7 = the least). Total scores fall between 18 and 126; the lower the score, the greater the need for help [28].

2.3. Interventions

A detailed description of the intervention has been published previously [22]. Patient safety was ensured by a geriatrician who assessed each participant's health status starting in the intervention group.

The home exercise group received a tailored exercise intervention at patients' homes for two one-hour sessions per week for one year. A physiotherapist administered the intervention, which was individually tailored to improve every-day skills while taking into account patients' needs. The group-based exercise intervention also trained for about one hour twice a week for one year. The visits to adult daycare centers lasted for four hours, of which the individual training time lasted one hour. Ten patients and two