JYU DISSERTATIONS 582

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Emphasis on Days Lived at Home, Utilization of Social and Health Care Services, Quality of Life, Physical Functioning, and Severity of Frailty

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND
HEALTH SCIENCES

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Esitetään Jyväskylän yliopiston liikuntatieteellisen tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston Liikunta-rakennuksen salissa L302
joulukuun 9. päivänä 2022 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä, in building Liikunta,
Auditorium L302 on December 9, 2022 at 12 o'clock noon.

JYVÄSKYLÄN YLIOPISTO
UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2022

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ISBN 978-951-39-9245-3 (PDF)
URN:ISBN:978-951-39-9245-3
ISSN 2489-9003

Permanent link to this publication: http://urn.fi/URN:ISBN:978-951-39-9245-3

ABSTRACT

Suikkanen, Sara
Home-based physical exercise among older adults with signs of frailty – Emphasis on days lived at home, utilization of social and health care services, quality of life, physical functioning, and severity of frailty
Jyväskylä: University of Jyväskylä, 2022, 89 p.
JYU Dissertations
ISSN 2489-9003; 582
ISBN 978-951-39-9245-3

Physical frailty is a syndrome in older adults which decreases functional capacity and quality of life and increases health care costs and the risks of institutionalization and mortality. The aim of this thesis was to evaluate the effects of a 12-month physiotherapist-supervised, home-based physical exercise program among community-dwelling older adults with signs of frailty on days lived at home, the utilization and costs of social and health care services, quality of life, functioning, and the severity of frailty.

The participants (n=300) were recruited in South Karelia, Finland. They were pre-frail (61%) or frail (39%) according to the frailty phenotype criteria, mean age was 83 y., and 75% were women. Participants were randomized into groups of 12-month, home-based exercise for 60 minutes twice a week (n=150) or usual care (n=150). The primary outcome, days lived at home, and the secondary outcome, the utilization and costs of social and health care services were assessed over 24 months using register information. Other outcomes were assessed at baseline, three, six and 12 months, and included: quality of life, functional independence, instrumental activities of daily living, physical performance, and number of falls. The home-based exercise included strength, balance, functional, and flexibility exercises, and was supervised by a physiotherapist.

The 12-month physical exercise program did not increase the number of days lived at home over the 24 months. The exercise intervention was cost neutral in the frail subgroup over 24 months, but increased costs among the pre-frail. The exercise intervention maintained the quality of life, improved physical performance, slowed down the deterioration of functional independence, and decreased the number of falls per person-year in comparison to usual care. The exercise intervention did not cause any severe adverse effects.

Keywords: older adults, frailty, physical exercise, rehabilitation, functioning, quality of life, cost-effectiveness

TIIVISTELMÄ (FINNISH ABSTRACT)

Suikkanen, Sara
Kotona toteutettu liikuntaharjoittelu gerasteenisilla ikääntyneillä – vaikutukset kotona-asumisaikaan, sosiaali- ja terveyspalveluiden käyttöön, elämänlaatuun ja toimintakykyyn sekä gerastenian vaikeusasteeseen.
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Gerastenia on ikääntyneillä esiintyvä oireyhtymä, joka heikentää toimintakykyä, elämänlaatua ja lisää terveydenhoitokustannuksia sekä kasvattaa tehostetun palveluasumisen ja kuoleman riskiä. Tämän tutkimuksen tavoitteena oli selvittää, millaisia vaikutuksia vuoden kestävällä fysioterapeutin ohjauksessa toteutetulla fyysisellä kotiharjoittelulla on gerasteenisten henkilöiden kotona-asumisaikaan, sosiaali- ja terveyspalveluiden käyttöön ja niistä koituviin kustannuksiin, elämänlaatuun, toimintakykyyn ja gerastenian vaikeusasteeseen.

Tutkittavat rekrytoitiin Etelä-Karjalan alueelta. Tutkittavista 61 %:lla oli gerastenian esiaste ja 39 %:lla gerastenia, keski-ikä oli 83 v. ja 75 % oli naisia. Tutkittavat (n=300) satunnaistettiin kahteen ryhmään: a) fysioterapeutin ohjaamaan kotiharjoitteluun (n=150) tai b) tavanomaiseen hoitoon (n=150). Vuoden kestänyt ohjattu liikuntaharjoittelu kahdesti viikossa 60 minuuttia kerrallaan piti sisällään lihaskunto-, tasapaino-, liikkuvuus- ja toiminnallisia harjoitteita. Päätulosmuuttuja, kotona-asumisaika, ja toissijaisista tulosmuuttujista sosiaali- ja terveyspalveluiden käyttötiedot kerättiin potilastietorekisteristä 24 kuukauden ajalta tutkimukseen satunnaistamispäivästä alkaen. Muita tulosmuuttujia olivat elämänlaatu, toiminnallinen itsenäisyys, välineelliset päivittäistoiminnot, fyysinen toimintakyky, ja kaatumisten lukumäärä. Niistä tiedot kerättiin haastattelemalla ja mittaamalla tutkittavat heidän kotonaan alussa, kolmen, kuuden ja 12 kuukauden kohdalla.

Verrattuna tavanomaiseen hoitoon, vuoden ohjattu liikuntaharjoittelu ei lisännyt kotona vietettyjä vuorokausia, mutta se ylläpiti elämänlaatua, paransi fyysistä suorituskykyä, vähensi kaatumisten määrä sekä hidasti itsenäisen toimintakyvyn heikkenemistä. Kun seurantavuoden sosiaali- ja terveyspalveluiden kustannukset otettiin huomioon, liikuntaharjoittelu oli kustannusneutraalia henkilöillä, joilla alkutilanteessa oli gerastenia. Pitkäkestoinen ohjattu liikuntaharjoittelu tulisikin jatkossa kohdistaa juuri heille.

Avainsanat: ikääntyneet, gerastenia, fyysinen harjoittelu, kuntoutus, toimintakyky, kustannusvaikuttavuus, elämänlaatu

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ACKNOWLEDGEMENTS

Finally, we're here! This adventure in the land of research and the quest for a PhD began in the summer of 2014 when I applied for the post of research physiotherapist in a new research project starting in the South Karelia Social and Health Care District. I am forever grateful to Markku Hupli, MD, PhD; Katriina Kukkonen-Harjula, MD, PhD; and Sanna Kääriä, PhD for their trust and decision to choose me to be part of their research team. I'll never forget that phone call I received from Markku while I was on the bus on the way to away game with my Finnish baseball team. The whole team sat there in silence and cheered so loudly when I told them "I got a job, and apparently, I´ll start a journey towards PhD". What a journey it has been. I was lucky to end up in the best possible research group I could ever have imagined.

My wonderful team of supervisors Professor Sarianna Sipilä PhD; Eeva Aartolahti, PhD; Katriina Kukkonen-Harjula, MD, PhD; and Assistant Professor Arto Hautala PhD, thank you for guiding me through this process and helping me navigate the sea of scientific journals and congresses and conduct the best possible research.

I would like to express my gratitude to the official reviewers of this thesis: Associate Professor Ellen Freiberger, PhD, from Friedrich Alexander University, and Professor Paolo Caserotti, PhD, from the University of Southern Denmark. And I would also like to thank Professor Hans Hobbelen, PhD from Hanze University of Applied Sciences for agreeing to be my opponent in the public defense of this thesis.

Every journey needs good company, and I was so lucky that Markku, Katriina and Sanna decided to choose Paula Soukkio, MSc as project manager of the HIPFRA research project. We orienteered our way through the forest of research challenges, and somehow, found all the checkpoints on the way. Sometimes we lost the map, or our feet got stuck in the mud, but we made it through. I just took a sprint at the end and crossed the finish line first, but I am 100% sure you'll also cross the finish line soon. Alongside my supervision team, Professor Kaisu Pitkälä has been an essential guide, giving me her time and bringing knowledge on the field of frailty and geriatrics to our research team – thank you Kaisu! Statistician Hannu Kautiainen, you were crucial to this project! We spent several hours at your house at Espoo, or via Zoom calls planning and conducting the analyses for our project. I have learnt so much from you. Our great research nurses Kaija Paajanen and Virpi Äärimaa; we had so much fun along the way. We would not have been able to recruit all the participants without your contribution. Thank you from the bottom of my heart that you were part of this amazing journey. I would also like to thank, all the Eksote's personnel who contributed their time and expertise for this research project along the way, especially all the homecare workers who fulfilled the screening forms and business intelligent analysts who extracted and tabulated the huge amount of register information for us. I really appreciate it. And Alice Lehtinen thank you for revising the English language of this thesis.

During this journey I learnt so much about research, but also about life itself. I am so grateful to all our participants, who opened up their homes and took part in this research project. I was lucky to meet almost all of you in person, so many amazing people, and to hear so many amazing life stories, receive so much advice for a good life, and to see the beautiful sceneries of cities, towns, and rural areas of South Karelia on my way to the assessment visits to your homes.

My wonderful colleagues at the University of Jyväskylä, especially Lilli’s six: Katariina Pirnes, MSc; Maarit Janhunen, MSc; Marjo-Riitta Anttila, MSc; Sari Honkanen MSc; and Mirjami Kantola, MSc – I am so thankful to have had the privilege to work with you. Our weekly Teams breaks were such important brief getaways, with lots of laughs and coffee. I am honored to have shared the roller-coaster ride of joys and frustrations with you. Without your peer support I don´t think I would ever have been able to finish this thesis.

I am grateful to have had so many amazing people in my corner outside the academic world, who cheered and encouraged me during this journey. All my aunts and uncles, thank you for your unconditional support and encouragement. I love sharing the joy of different hobbies, such as photography, literature, playing cards, or even learning Spanish, with you. My friends Johanna, Mari, Carla, and Saila, would you ever have imagined back in the day that I was the one who ended up doing a PhD thesis? I know, I wouldn´t either. But here I am. Thank you for all your support and help, for clearing my head and ventilating my thoughts when I needed it most. Eero, I am so very grateful to have you in my life. Thank you for being the essential motor rotor that kept me going through the stormy seas, gravel traps, and frustrations on my way to this point. I hope I can be the same for you, and push you forward on your PhD journey.

I want to express my deepest gratitude to my parents Kirsi and Arto and my sister Aija. You have taught me to never give up and to compete fairly, and you never stop believing in me. The encouragement yelled from the stands of the Finnish baseball field where I could never catch one single ball “You’ll catch the next one, or the next one, or the one after that, just don’t quit and keep trying, eventually you’ll catch one,”… has been useful advice to remember, not only on the Finnish baseball field, but also in the field of academia. I’ll never forget it.

And finally, my god daughters Miisa, Elsi, Elea and Helmi: I hope I can encourage you to grab every opportunity with both hands, and to follow you dreams, wherever they may lead you. I will try to be there for you and guide and cheer you on your individual journeys. Keep going, don’t stop trying, and eventually you’ll get there.

Lappeenranta, October 2022
Sara

ORIGINAL PUBLICATIONS AND AUTHOR CONTRIBUTION

The thesis is based on the following publications, which will be referred to by their Roman numerals. The thesis also includes unpublished data.

I Suikkanen, S., Soukkio, P., Pitkälä, K., Kääriä, S., Kautiainen, H., Sipilä, S., Kukkonen-Harjula, K., & Hupli, M. (2019). Older persons with signs of frailty in a home-based physical exercise intervention: baseline characteristics of an RCT. *Aging Clinical and Experimental Research, 31*(10), 1419–1427. doi.org/10.1007/s40520-019-01180-z

II Suikkanen, S. A., Soukkio, P. K., Aartolahti, E. M., Kautiainen, H., Kääriä, S. M., Hupli, M. T., Sipilä, S., Pitkälä, K. H., & Kukkonen-Harjula, K. T. (2021). Effects of home-based physical exercise on days at home and cost-effectiveness in pre-frail and frail persons: randomized controlled trial. *Journal of the American Medical Directors Association, 22*(4), 773–779. doi.org/10.1016/j.jamda.2020.06.005

III Suikkanen, S., Soukkio, P., Aartolahti, E., Kääriä, S., Kautiainen, H., Hupli, M. T., Pitkälä, K., Sipilä, S., & Kukkonen-Harjula, K. (2021). Effect of 12-month supervised, home-based physical exercise on functioning among persons with signs of frailty: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation, 102*(12), 2283–2290. doi.org/10.1016/j.apmr.2021.06.017

IV Suikkanen, S., Soukkio, P., Kautiainen, H., Kääriä, S., Hupli, M. T., Sipilä, S., Pitkälä, K., Aartolahti, E., & Kukkonen-Harjula, K. (2022). Changes in the severity of frailty among older adults after 12 months of supervised home-based physical exercise: a randomized clinical trial. *Journal of the American Medical Directors Association, 23*(10), 1717.e9–1717.e15. doi.org/10.1016/j.jamda.2022.07.010

This doctoral thesis consists of four articles that used data from the HIP Fracture and FRAilty (HIPFRA) randomized controlled trial (ClinicalTrials.gov NCT02305433). The original research plan for the HIPFRA study was written by Markku Hupli, MD, PhD; Sanna Kääriä, PhD; and was finalized by Katriina Kukkonen-Harjula, MD, PhD; Paula Soukkio, MSc, and Sara Suikkanen, MSc. Suikkanen started as a research physiotherapist at the South Karelia Social and Health Care District at the beginning of the HIPFRA research project and took part in drafting the ethical approval application and trial registration. Suikkanen also participated in the data collection and was responsible for data file construction and for saving the collected data in the role of data manager. Advanced statistical analyses were performed with experienced statistician Hannu Kautiainen. Suikkanen wrote the first drafts of manuscripts I–IV and finalized them according to the co-authors' suggestions and comments.

FIGURES

TABLES

ABBREVIATIONS

15D	15-Dimensional quality of life measure
ADL	Activities of Daily Living
ATP	Adenosine Triphosphate
BI	Business Intelligence
BMI	Body Mass Index
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CES-D	Center of Epidemiology Studies Depression scale
CFS	Clinical Frailty Scale
Eksote	South Karelia Social and Health Care District
EUR	Euro, €
FRAIL	Fatigue, Resistance, Ambulation, Illnesses, Loss of weight
FROP-Com	Falls Risk for Older People in the Community
FIM	Functional Independence Measure
GAS	Goal Attainment Scale
HIPFRA	HIP Fracture and FRAilty -study
HRQOL	Health-Related Quality of life
IADL	Instrumental Activities of Daily Living
ICER	Incremental Cost-Effectiveness Ratio
ICF	International Classification of Functioning, Disability and Health
IQR	Inter Quartile Range
IRR	Incidence Rate Ratio
kcal	Kilocalories
Kela	The Social Insurance Institution of Finland (Kela)
kg	Kilogram
m/s	Meters per second
MET	Metabolic Equivalent
MMSE	Mini-Mental State Examination
MNA	Mini Nutritional Assessment
QALY	Quality Adjusted Life Year
QOL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relative mean Ratio
RM	Repetition Maximum
ROM	Range of Motion
RPE	Ratings of Perceived Exertion
s	Second
SD	Standard deviation
SE	Standard error
SPPB	Short Physical Performance Battery
VO_2 max	Maximal oxygen consumption
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

The number of older adults is rising globally, as more and more people are living over the age of 60 years. In 2020, 727 million people were aged 65 or over and this number will increase rapidly in the next few decades (United Nations, 2020). Some diseases and conditions are more common among older adults than younger populations, the so-called geriatric giants, which originally included instability, immobility, intellectual impairment, and incontinence (Morley, 2004). Nowadays, the geriatric giants include frailty, sarcopenia, anorexia of aging, and cognitive impairment, all of them increases the risks of falls and osteoporotic fractures, depression, and delirium (Morley, 2017).

The increasing number of older adults impacts on countries' economic statuses as their consumption and productivity are unbalanced (United Nations, 2020). Finland´s social and health care service system is also facing this challenge. In the aging population, the need for care increase with age, and most health care expenses are concentrated in the last years of life (Yang et al., 2003). The living arrangements of older adults depend on their health constraints, functional capacity, financial resources, and kin availability, as well as on cultural norms and traditions (United Nations, 2020). In western Europe, including Finland, older adults mainly live alone or with their spouses (United Nations, 2020). If the ability to survive at home is at risk, the person can obtain homecare services from their health care provider. In 2020 in Finland, the number of homecare visits was around 40 million, and over half of these were to people aged 85 or older (Saukkonen et al., 2021).

As one of the geriatric giants, frailty is an important medical syndrome among older adults. It reduces a person's ability to handle stressors such as infections and it diminishes their functional capacity, which can lead to dependency on others (Clegg et al., 2013). Among those who are frail, the risk for falls, and need for care is higher, and can lead to being unable to continue living at home (Clegg et al., 2013). Frailty also increases the risk of hospitalization and mortality (Clegg et al., 2013). The increased need for care also raises the costs of social and health care services. For example, annual health care costs for women who are frail can be 2.6 times higher than those for women who are not frail (Ensrud et al., 2018).

One of the key components of promoting older adults' functional ability and tackle frailty is physical activity. World Health Organization (WHO)´s physical activity guidelines recommend that older adults should have 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity per week, accompanied by strength, balance, and flexibility exercises twice a week (Bull et al., 2020; Izquierdo et al., 2021). However, these recommendations are seldom achieved by older adults, especially those with chronic diseases or who are frail. Older adults may feel that they do not have the mental or physical capacity or knowledge to be physically active (Franco et al., 2015). Transportation, costs, fear of falling, or feeling that physical training is unsafe without supervision (Franco et al., 2015) and even previous unenjoyable experiences of physical exercise, fatigue, and bad weather (Cohen-Mansfield et al., 2003) can become barriers that reduce older adults' motivation to be physically active and decrease their sedentary time. Among community-living older adults, the average time spent being sedentary is 65–80% of waking hours (Harvey et al., 2015). Sedentary behavior is defined by spending time in a sitting, reclining, or lying posture, with a low energy expenditure (≤ 1.5 metabolic equivalents, METs) (Tremblay et al, 2017). Most sedentary time on older adults occurs indoors at home, especially when they are alone, or during leisure time during transportation (Leask et al., 2015).

As we are facing a growing population of older adults and an increased need for their care in the future, it is important to find effective ways to help older adults live in their homes longer. The Finnish government has set improved functional capacity of older people, a higher number of active life years, and shorter average time needed for intensive care and nursing as objectives for 2030 (The Ministry of Social Affairs and Health, Finland, 2020). To be able to achieve these objectives, it is important to find successful and cost-effective ways to promote physical activity and engage older adults to exercise regularly, especially those who are frail.

2 REVIEW OF THE LITERATURE

2.1 Frailty

The concept of frailty has evolved considerably since the 1970s (Abellan Van Kan et al., 2008). The term "frail" was first used to describe a person who was institutionalized, and then those who failed to thrive and were dependent on others in activities of daily living (ADL) (Abellan Van Kan et al., 2008). In the mid-1990s, frailty shifted more towards the concepts we know today. Nowadays, frailty is described as a geriatric syndrome in which the dysregulation of multiple physiologically and biologically interconnected systems crosses a threshold and compromises the homeostasis of the body (Fried et al., 2021). The key systems in which dysregulation can be linked to emerging frailty are the stress response, metabolism, and musculoskeletal systems (Fried et al., 2021). Frailty increases vulnerability with diminished strength, endurance, and physiological functions, and with decreased reserves and resistance to stressor events (Clegg et al., 2013; Fried et al., 2001; Morley et al., 2013). Experts in the field still have no clear consensus on a single definition (Rodríguez-Mañas et al., 2013) to use as a standard diagnostic criterion for frailty (Dent et al., 2016). At the moment, the concepts most used in research to define and measure frailty are physical phenotypical frailty (Fried et al., 2001) and the accumulation of deficits model (Mitnitski et al., 2001). For the clinical screening the Fatigue, Resistance, Ambulation, Illness and Loss of weight (FRAIL)-questionnaire (Abellan van Kan et al., 2008; Morley et al., 2012), or the Clinical Frailty Scale (CFS) (Rockwood et al., 2005) can be used. In this thesis, the frailty perspective is based on phenotypical physical frailty.

2.1.1 Frailty phenotype

The five frailty phenotype criteria: weight loss, exhaustion, low physical activity, slowness, and weakness, which measure physical frailty, were introduced in 2001 by Fried et al. (2001). The criteria are based on the theoretical model of frailty cycle (Figure 1) (Fried et al., 2001). A person is classified as frail if they fulfill three or more criteria, and pre-frail if they meet one or two (Fried et al., 2001).

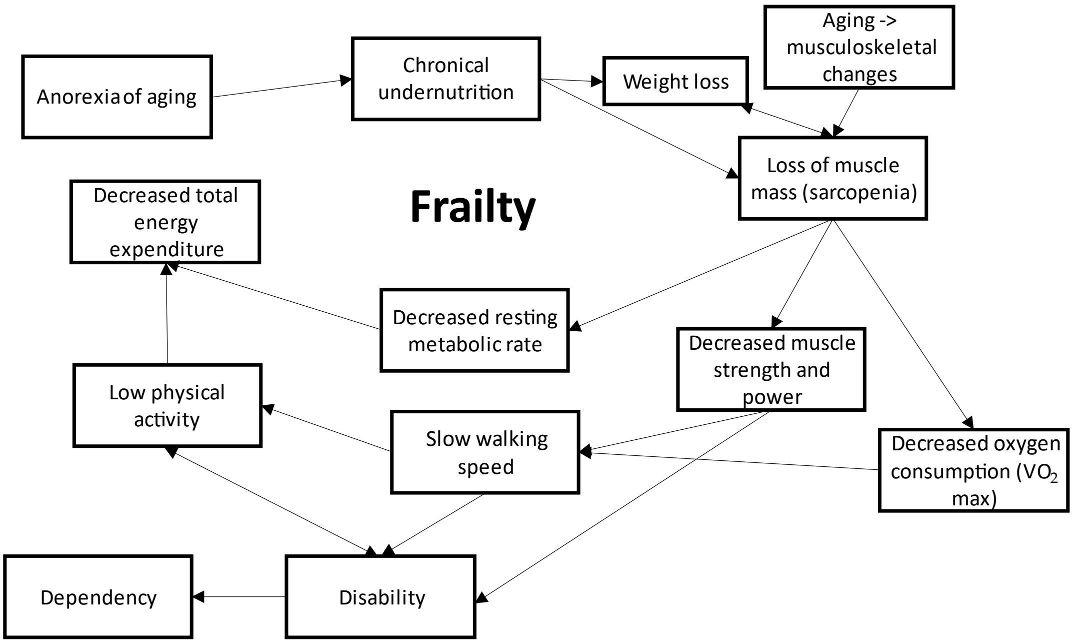

FIGURE 1 Frailty cycle modified from Fried et al. (2001).

2.1.1.1 Weight loss

This frailty phenotype criterion originates from anorexia of aging and chronic undernutrition. Weight loss in older adults is a sign of catabolism and macronutrient deficiency, and older adults are more prone to disease-related weight loss than younger people (Norman et al., 2021). Anorexia of aging is described as a loss of appetite and/or decreased food intake because of medications, chronic diseases, and neurodegenerative conditions (Landi et al., 2016; Merchant et al., 2022). The deterioration of the sense of smell and taste (Sanford, 2017), hormonal changes (Landi et al., 2016), changes in fundus of the stomach and decreased antral stretch (Morley, 2017) as well as chronic low-grade inflammation and circulating cytokines (Landi et al., 2016; Morley, 2017) cause loss of appetite and the development of anorexia of aging. The risk factors for malnutrition in older adults are excessive polypharmacy, decline in physical function, cognition, and health, loss of interest in life, and problems in swallowing (Fávaro-Moreira et al., 2016). Anorexia of aging is a risk factor for weight loss and can lead to loss of muscle mass and strength (Sanford, 2017). Malnutrition also has a negative effect on muscle mass, muscle strength and physical performance (Lengelé et al., 2021), slows down the recovery process from different diseases and increases morbidity and mortality risks (Norman et al., 2021). The weight loss criterion in the frailty phenotype is defined as unintentional weight loss of more than 4.5 kg (10 pounds) or over 5% of body weight compared to previous year's weight (Fried et al., 2001).

Weight loss seems to be the last criterion to occur (Stenholm et al., 2019) and is often the least prevalent criterion among frail older adults (Fried et al., 2001; Op het Veld et al., 2015; Xue et al., 2008).

2.1.1.2 Weakness

During the aging process, the reserves of physiological systems begin to gradually deteriorate, which leads to deterioration of muscle mass and strength (López-Otín et al., 2013). The loss of muscle strength is two to five times greater than loss of muscle mass in older adults (Delmonico et al., 2009). For example, after the age of 75, the loss of muscle mass among women is 0.64–0.70% and among men 0.80–0.98% per year, and the loss of muscle strength 2.5–3% and 3–4%, respectively (Mitchell et al., 2012). In short, a muscle produces force by contracting the muscle fibers, which are regulated by stimuli from motor units and powered by adenosine triphosphate (ATP) (de Rezende Pinto et al., 2015). Muscles' plasticity requires complex molecular mechanisms (de Rezende Pinto et al., 2015) and if it is disturbed or imbalanced, it can lead to loss of muscle mass and strength (Cruz-Jentoft & Sayer, 2019). Muscle strength deterioration is the consequence of neural and muscular changes in the aging body (Manini & Clark, 2012). The deterioration of motor unit recruitment and fiber type transformation from fast to slow, together with loss of muscle mass, affected by low physical activity and low protein intake are key contributors to the loss of muscle strength in older adults (Clark & Manini, 2010; Manini & Clark, 2012). When the loss of muscle mass is faster than the normal process, the condition is called sarcopenia (Cruz-Jentoft & Sayer, 2019).

Sarcopenia and frailty are closely related, and sarcopenia has been seen as a substrate to frailty (Cruz-Jentoft & Sayer, 2019). In frailty, the loss of muscle strength is more substantial than in the normal aging process (Fried et al., 2001; Clegg et al., 2013). The weakness criterion assesses the loss of muscle strength and is measured by handgrip strength. The criteria values are adjusted for sex and body mass index (BMI) and are based on the lowest 20% of the participants in the Cardiovascular Health Study (Fried et al., 2001). Weakness is the most commonly met criterion among older adults (Fried et al., 2001; Op het Veld et al., 2015; Xue et al., 2008).

2.1.1.3 Slowness

In frail older adults, dysregulation of physiological systems (Fried et al., 2021), and loss of muscle strength (Manini & Clark, 2012) can also emerge in the form of slow gait speed. Walking is a complex motor task that requires the co-operation of physiological systems such as the central and peripheral nervous system, the perceptual system, muscles, bones, joints, and energy production/delivery (Ferrucci et al., 2000). Impairments and malfunctioning in these systems can lead to walking limitations and disabilities. Slow gait speed can predict adverse outcomes (Abellan van Kan et al., 2009; Guralnik et al., 2000). Walking speed below 0.8m/s seems to be the pace that predicts median life expectancy, while faster walking speeds predict longer and slower walking speed shorter time of survival among older adults (Studenski et al., 2011). In the original phenotype criteria, the threshold for slowness was defined by the lowest 20% walking time on 15 ft (4.57 meters), adjusted for gender and height (Fried et al., 2001). Measuring gait speed is quite a simple, inexpensive measurement to perform on older adults. The slowness criterion is quite often modified in research on frail older adults (Theou et al., 2015). Studies have also used different cutoffs and distances to assess slowness (Theou et al., 2015).

2.1.1.4 Low physical activity

Low physical activity and sedentary behavior among older adults are not uncommon, even though physical activity has many good indications for enhancing health (Izquierdo et al., 2021). Physical activity is defined in WHO´s physical activity guidelines as "any bodily movement produced by skeletal muscles that requires energy expenditure" (World Health Organization, 2020). By being physically active, older adults can reduce their risk of functional limitations (Bull et al., 2020), as low physical activity is associated with lower functional independence (Paterson & Warburton, 2010), higher prevalence of frailty, and more severe frailty (Kehler et al., 2018), increased risks of all-cause mortality, ADL disabilities, risks of falling, cognitive decline, and depression (Cunningham et al., 2020).

Older adults may have false beliefs and feel that age-related deterioration of functioning is inevitable and that physical exercises might be harmful or dangerous for their health condition (Franco et al., 2015). Different kinds of physical limitations; comorbidities; concerns of falling, pain, and discomfort; and deteriorating health can become mental barriers to being physically active (Cohen-Mansfield et al., 2003; Franco et al., 2015).

Low physical activity, Fried et al.´s (2001) original criterion, was determined by estimating the energy expenditure by kilocalories (kcal) expended per week, and was based on the short version of the Minnesota Leisure Time Activity Questionnaire. Energy expenditure per week is calculated using a standardized algorithm for walking, chores (moderately to strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, and swimming (Fried et al., 2001; Taylor et al., 1978). The low physical activity criterion is often modified in the frailty research, as the Minnesota Leisure Time Activity Questionnaire is quite long, its evaluation is lengthy, and it has some limitations when used on older adults (Theou et al., 2015) such as the large floor effect (Theou et al., 2012). Different studies have used questions on the amount of physical activity, or how often the person is physically active rather than energy expenditure (Theou et al., 2015).

2.1.1.5 Exhaustion

In the frailty phenotype, the exhaustion criterion represents poor endurance and energy (Fried et al., 2001). It is elicited by questions on how often a person feels that "everything I did was an effort" and/or "I could not get going". These questions are from Center of Epidemiology Studies Depression scale (CES-D) (Orme et al., 1986). According to Fried et al. (2001), these questions on exhaustion are associated with graded exercise testing and maximal oxygen consumption (VO_2 max). Exhaustion is also closely related to depression and fatigue. Depression in older adults has a negative impact on mental functioning, dementia, and cognitive impairment, quality of life, disability, and mortality (Hitchcock Noël et al., 2004; Rodda et al., 2011). Fatigue is also a health problem for older adults, as it has attributes of low energy levels, an early indicator of disability, and impairment of daily activities (Su et al., 2022). It also reduces quality of life (QOL) and compromises the outcomes of other health problems (Yu et al., 2010).

2.1.2 Other frailty measures

Alongside frailty phenotype, another commonly used method to detect frailty is a frailty index (Dent et al., 2016). This is based on the accumulation of different health deficits, symptoms, signs, disabilities, and diseases, for which an index is calculated on the basis of whether a person has them or not (Mitnitski et al., 2001; Rockwood & Mitnitski, 2007). Number of deficits person has, are divided by the number of deficits assessed. It scores a value between 0 (no deficits) and 1 (maximal number of deficits) (Mitnitski et al., 2001; Rockwood & Mitnitski, 2007). If the index score is between 0.1 and 0.21, the person is pre-frail, and if it is over 0.21, the person is considered frail and at risk of adverse outcomes (Hoover et al., 2013). A frailty index can also be calculated from the data of the Comprehensive Geriatric Assessment (CGA) (Jones et al., 2004). CGA is a multidimensional and multidisciplinary process, which is used to detect needs of older adults (e.g., medical, psychological, social, and functional) and co-ordinate an integrated care plan for the individual to meet those needs (Parker et al., 2018). Clinical Frailty Scale (CFS) is based on clinical judgment of for example physician or other health care professional (Rockwood et al., 2005; Rockwood & Theou, 2020) and is used mostly for clinical screening (Dent et al. 2016). It has nine-point scale with written description and visual chart of persons with different severities of frailty, ranging from 1 (very fit) to 9 (terminally ill) (Rockwood et al., 2005; Rockwood & Theou, 2020).

2.2 Prevalence of frailty

The variation in the prevalence of frailty in different studies is considerable, as the studied populations and different diagnostic methods used for assessing frailty vary greatly (Collard et al., 2012; O'Caoimh et al., 2021). There is no golden standard for assessing frailty (Dent et al., 2016), and many studies use modified criteria of frailty phenotype (Theou et al., 2015) or different deficit lists to calculate the frailty index (Searle et al., 2008). A systematic review of data from 62 countries, estimated that the prevalence of frailty among people aged 50 or over was 12% and that of pre-frailty 46% when measured using frailty phenotype, 24%

and 49%, respectively when using the accumulation of deficit model (O'Caoimh et al., 2021).

Frailty can appear in individuals in different ways, as people can have many combinations of phenotype criteria and deficits (Xue et al., 2008). As the two ways of assessing frailty using the phenotype criteria or frailty index are different in their basic concepts, they may also detect different people as frail and should be used as compliments rather than comparisons (Cesari et al., 2014). When the two concepts were used in the same population, the agreement between them was poor (Blodgett et al., 2015) or fair (Zhu et al., 2016). In a study of adults aged over 65, the prevalence of frailty was similar when either the frailty index (8%) or phenotype criteria (7%) were used. However, only 12% of the individuals were classified as frail on the basis of agreement with both concepts (Xue et al., 2020).

The prevalence of frailty increases with age (Hoogendijk et al., 2019) and almost one third of people over 80 years are frail (Hoogendijk et al., 2019). Frailty is more common among women than men (Collard et al., 2012; Hoogendijk et al., 2019). It is a dynamic process, and its severity can fluctuate over time (Gill et al., 2006; Kojima et al., 2019; Ofori-Asenso et al., 2020). Pre-frailty can redispose a person to developing frailty but does not always proceed to the frailty state (Sezgin et al., 2022). However, it more commonly becomes severe than shifts to a robust state (Gill et al., 2006; Kojima et al., 2019). The prevalence of physical frailty in individuals aged over ≥50 also differs between continents: In Africa, the prevalence was 22%, in the Americas 17%, and in Europe 8% (O'Caoimh et al., 2021). However, the data used from different regions were quite heterogenous and limited. In Europe, the prevalence of physical frailty is also higher in southern than in northern parts of the continent (Santos-Eggimann et al., 2009).

2.3 Functioning and frailty

Functioning includes physical, psychological (including cognition), and social dimensions, which are all important aspects for maintaining a person's functional capacity and independence in daily tasks. The deterioration of functioning can lead to disability, and the scheme of disablement process was first introduced by Nagi (1976) and developed further by Verbrugge & Jette (1994). They added extra-individual (e.g., medication, environment, rehabilitation) and intra-individual risk factors (e.g., psychological attributes, lifestyle) to the disablement model to make it more comprehensive. The disablement model (Figure 2) shows how pathology or diseases cause physiological abnormalities as signs and symptom (e.g., loss of muscle mass). These abnormalities/diseases can lead to impairments, which emerge as dysfunctions in organ systems (e.g., reduced strength). Dysfunction in organ systems causes functional limitation, which manifests as difficulties performing physical and/or cognitive tasks (e.g., difficulties walking stairs). Inability to perform ADL can eventually lead to disability (e.g., being unable to leave home) (Espinoza et al., 2018). The disablement process is affected by personal, extra-individual and intra-individual factors such as lifestyle, psychosocial attributes, and physical activity (Verbrugge & Jette, 1994). Extra-individual factors such as rehabilitation, medication, and external support (e.g., homecare services), can slow down or even reverse the disablement process (Verbrugge & Jette, 1994). A person's built, physical, and social environments (Verbrugge & Jette, 1994) are important, as they can either enable or prevent the person from functioning at their full capacity.

Frailty is a contributing factor in the disablement process; it is not a synonym for disability, even though these two can overlap (Fried et al., 2004). In the disablement process, each stage increases the risk of frailty, and frailty increases the risk of further advancing towards disability (Espinoza et al., 2018). The third component that can overlap with disability and frailty is multimorbidity (Fried et al., 2004). In multimorbidity, the person has two or more concurrent diseases, and each can increase the cumulative burden and severity of the other (Marengoni et al., 2011). Most people who are frail are also multimorbid, but a minority of people with multimorbidity are frail (Vetrano et al., 2019). Multimorbidity can cause complex health problems that may lead to impairments and functional limitations (Marengoni et al., 2011). Figure 2 presents the relationships between frailty, the disablement process and multimorbidity, and the factors that affect them.

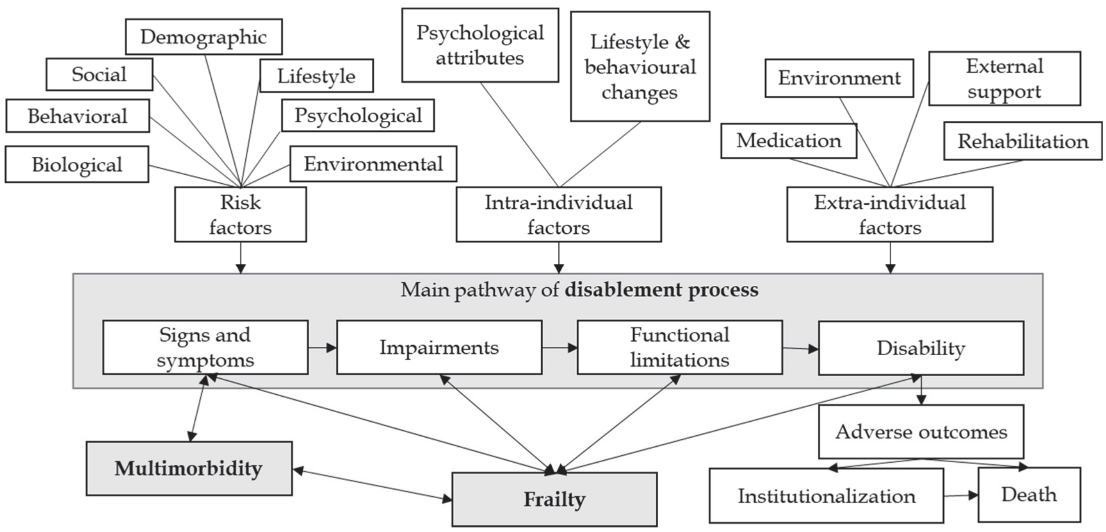

FIGURE 2 Frailty, multimorbidity and disablement process. Modified from Verbrugge & Jette (1994), Fried et al. (2004), and Espinoza et al. (2018).

One way to classify functioning is the International Classification of Functioning, Disability, and Health (ICF) framework (Figure 3). This highlights the aspects that influence a person´s functioning and other components that may cause disability (World Health Organization, 2013). In ICF, functioning is based on body functions, body structures, activities, and social participation, and indicates the interaction between the individual's health condition and environmental and personal factors (World Health Organization, 2013). The frailty phenotype criteria can be classed under body functions and structures (e.g., grip strength), activities (e.g., physical activity), and participation domains of the ICF framework (Azzopardi et al., 2016).

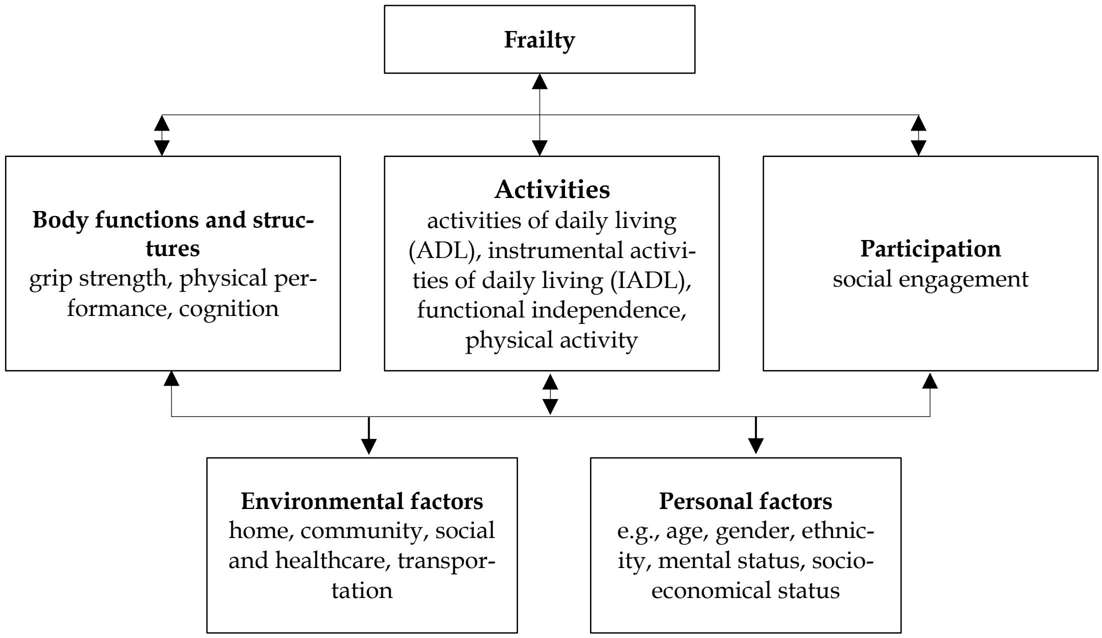

FIGURE 3 Frailty in the International Classification of Functioning, Disability, and Health (ICF) framework.

Body functions include physiological and psychological functions of the body systems, such as physical performance and cognition, whereas body structures include organs, bones, and muscles (World Health Organization, 2013). Muscular, skeletal, and neurological systems work together to produce a wide variety of bodily movements, which can vary in speed and strength depending on the task at hand (Tieland et al., 2018).

Physical performance can be described as an "objectively measured whole body function related with mobility" (Beaudart et al., 2019). It is a multidimensional concept that requires co-operation between body functions and systems such as muscles, bones, balance, cardiovascular and neurological inputs, and motivation (Beaudart et al., 2019). The loss of physical performance leads to disability and dependence over time (Fried et al., 2021). A decline in physical performance is associated with falls (Lauretani et al., 2019), nursing home admissions (Guralnik et al., 1994) and all-cause mortality (Pavasini et al., 2016). For example, low handgrip strength among older adults is associated with higher risks of disability and mortality (Bohannon, 2008).

Among older adults, other important aspects of functioning and activities are cognitive decline, pain, depression, and multimorbidity (multiple medications), which can lead to impaired functional ability in ADLs and IADLs (Connolly et al., 2017). Cognition includes domains such as sensation, perception, attention, concentration, memory, executive functioning, processing speed, and language and verbal skills (Harvey, 2019). Even though the prevalence of mild cognitive impairments and dementia is higher in the aging population, they are not part of normal aging (World Health Organization, 2012). The normal aging process might cause subtle changes in a person's cognitive functions of conceptual reasoning, memory, and processing speed (Harada et al., 2013). Among non-demented people, those with frailty tend to have worse cognitive functioning than pre-frail and non-frail people (Sleight & Holtzer, 2020).

In the framework of healthy ageing the persons functional ability is determined by interaction between the individual's intrinsic capacity, and environment (Beard et al. 2016; Cesari et al., 2018). This concept of intrinsic capacity is based on the ICF model (Cesari et al., 2018). Intrinsic capacity includes five domains; locomotion (mobility, gait, balance, muscle strength), cognitive (intelligence, memory), psychological (mood, emotional vitality), and sensory (hearing, vision) capacities, and vitality (hormonal function, energy metabolism, cardio-respiratory function) (Beard et al., 2022; Cesari et al., 2018;).

Good physical and psychological functioning are key components of a person's ability to perform and execute different activities and tasks in their daily lives (Beaudart et al., 2019). The basic ADLs are transferring (from one body position to another), eating, dressing, personal hygiene, and going to toilet (maintaining urinary and fecal continence) (Katz et al., 1963). More complex ADLs are Instrumental Activities of Daily Living (IADL), such as using the telephone, shopping, preparing meals, housekeeping, doing laundry, using transportation, taking care of medication, and handling one's own finances (Lawton & Brody, 1969). The number of older adults with some limitations to their ADL or IADL functions begins to rise after they turn 70 (Chatterji et al., 2015). Older adults with signs of frailty are more likely to have difficulties in basic ADL and/or IADL functions than same-aged robust people (Rochat et al., 2010). Impaired functional capacity can lead to the inability to perform and maintain functional independence (Izquierdo et al., 2021). Mild cognitive impairment and dementia can have a negative effect on the IADL tasks that require higher cognitive processing such as finances, using the telephone and taking care of one's own medications (Jekel et al., 2015). If a person wants to live at home independently, they have to be able to handle both basic and instrumental ADLs. With environmental support, a person may be able to cope with IADL and ADL functional difficulties (Altman, 2014) and live at home for longer.

2.4 Quality of life and frailty

In the medical and health sciences literature, the term quality of life (QOL) has been defined in many ways and there is no clear consensus on its definition (Post, 2014). Most often, QOL is seen as a multidimensional concept that includes health, physical well-being, functional ability, and emotional and social domains (Tulsky & Rosenthal, 2002). In relation to QOL, the term health-related quality of life (HRQOL) has been used, but its definition is complex, and it can be seen as entangled with QOL, health, and the value of health (Karimi & Brazier, 2016). Older adults with physical frailty seem to have lower QOL than robust people (Henchoz et al., 2017; Kojima et al., 2016). This association can be partly explained by the characteristics of poor health (Henchoz et al., 2017) and smaller social networks (Hoogendijk et al., 2016).

When frail older adults were asked what aspects of their lives had the most impact on their QOL, they named a combination of health, well-being, and social interactions as the most important factors (Puts et al., 2007). Poor physical health influences social activities and can lead to isolation and loneliness (Puts et al., 2007), which increase the risks of more severe frailty (Gale et al., 2018; Sha et al., 2020). The health and mobility aspects of QOL have the clearest associations with physical frailty (Henchoz et al., 2017). The QOL of older adults with frailty has only improved with interventions that also improved some physical outcomes (Campbell et al., 2021).

Changes in QOL can be used to calculate the value of life years (Whitehead & Ali, 2010). In health economics, Quality-Adjusted Life Years (QALY) is used as an outcome measure to evaluate and guide allocations of health care resources, by evaluating interventions and health improvements (Weinstein et al., 2009). QALY can combine mortality, morbidity, and perfect health in a single index and can be calculated from QOL measures, which provides an index between 0 (death) to 1 (perfect health) (Whitehead & Ali, 2010). QALY is an interval scale in which a gain from 0.2 to 0.3 is equally valuable as a gain from 0.6 to 0.7 (Weinstein et al., 2009). QALYs are used in calculations of the Incremental Cost-Effectiveness Ratio (ICER), in which treatment alternatives can be evaluated according to the costs and their effectiveness to QALY (Bambha & Kim, 2004). ICER is calculated from the costs and QALYs of the intervention treatment group and control treatment/usual care group using the following formula:

$$\text{ICER} = \frac{costs\ (€)^{\ treatment} - \text{costs}(€)^{control}}{QALY^{treatment} - QALY^{\ control}}$$

2.5 Utilization of social and health care services and frailty

Aging increases the probability for need for care, and most health care expenses are concentrated in the last years of life (Yang et al., 2003). This is due to the aging process, which causes physiological systems to gradually deteriorate (López-Otín et al., 2013), and increases the probability of multimorbidity (Calderón-Larrañaga et al., 2017). In robust older adults, a minor illness, for example urinary tract infection, causes a momentary decline in functional capacity, and after a while the patients recover back to their previous state (Clegg et al., 2013). After a stressor event, a frail individual's ability to maintain homeostasis of the body´s interconnected physiological and biological systems decreases (Fried et al., 2021). The same infection in frail people causes greater deterioration in functioning, and recovery takes a longer time than in robust people. Moreover, they may not recover back to their previous functional state at all (Clegg et al., 2013; Fried et al., 2021).

The odds of being hospitalized (Chang et al., 2018; Kojima et al., 2016; Sirven & Rapp, 2017) are 1.2 times higher for pre-frail and 1.9 times higher for frail than robust people (Ilinca & Calciolari, 2015). As frailty prolongs the recovery process, the lengths of stays in hospital wards are longer for frail than robust people (Evans et al., 2014; Khandelwal et al., 2012;). The severity of frailty also affects the discharge location after acute care, as the less frail are more likely sent home and people with more severe frailty are discharged to rehabilitation centers and primary care wards, or home with the help of homecare services (Evans et al., 2014; Rose et al., 2014). Frail people are also at a higher risk of rehospitalization within six months of discharge (Comans et al., 2016) and make more visits to emergency departments (Hoeck et al., 2012) than robust people. If surgical operations are needed, frailer people are at a higher risk of needing institutionalized care after their operation (Robinson et al., 2011), and patients with severe frailty are more likely be discharged to a nursing home than robust patients (Evans et al., 2014; Rose et al., 2014).

Not only those hospitalized, but also people with signs of frailty can have difficulties maintaining their functional capacity and ability to function independently at home, so they use more services that help them with meals and household duties (Rochat et al., 2010) and have higher odds of being admitted to a nursing home than robust people (Kojima, 2018). People who are malnourished and frail have a lowest survival rate (Wei et al., 2018).

Through the increased need for care, more severe frailty associates with higher costs (Bock et al., 2016; Ensrud et al., 2018; García-Nogueras et al., 2017; Hajek et al., 2018; Ilinca & Calciolari, 2015). In addition to higher risks of hospitalization and nursing home placements, people with signs of frailty also have more contacts with homecare personnel, general practitioners (Hoeck et al., 2012), and physiotherapists (Rochat et al., 2010). Frail people's greater contacts with health care professionals increase the costs of health care service utilization almost three times more than those of robust people (Ensrud et al., 2018; Ilinca & Calciolari, 2015), independently of multimorbidity status (Bock et al., 2016; Ensrud et al., 2018). Meeting all five frailty criteria increases the risk of mortality (Salminen et al., 2020; Xue et al., 2021).

2.6 Management of frailty

2.6.1 Exercise related methods

The evidence shows that physical exercise might prevent physical frailty (Oliveira et al., 2020), but those who are already frail or pre-frail spend most of their time in sedentary positions such as sitting, reclining, or lying down (Kehler et al., 2018) and do not adhere to WHO's physical activity guidelines. Physical frailty is assessed using five phenotype criteria of weight loss, weakness, exhaustion, slowness, and low physical activity levels (Fried et al., 2001), all of which are the consequence of the dysregulation of bodily systems and may be prevented by physical exercise and being physically active (Fried et al., 2021).

Over the last decade, several systematic reviews and meta-analyses of exercise programs and the management of frailty and their effects on functioning have been published (Apóstolo et al., 2018; Dedeyne et al., 2017; Giné-Garriga et al., 2014; Kidd et al., 2019; de Labra et al., 2015; Travers et al., 2019). The systematic reviews conclude that physical exercise training could improve some aspects of physical functioning (Giné-Garriga et al., 2014; de Labra et al., 2015) and have found evidence that the physical performance of frail older adults can be improved by tailored, supervised, exercise interventions (Kidd et al., 2019). Multicomponent physical exercise with a resistance training component seems to most strongly support frailty management (Dent et al., 2019). Alongside resistance training, exercise should include balance, aerobic, and flexibility exercises (Jadczak et al., 2018).

Physical training programs for frail older adults can take place in different kinds of environments: hospitals, rehabilitation centers, at home, or in community centers and gyms (Li et al., 2022). Group-based exercise programs have a positive impact on frail older adults' physical performance (Langlois et al., 2013; Tarazona-Santabalbina et al., 2016). In a systematic review, center-based exercise programs had slightly better results in lower limb strength, and in the Timed up-and-go test than home-based exercise among older adults (Li et al., 2022). However, the home-based exercise was mainly performed unsupervised, whereas the center-based exercise was supervised. If the exercise program sessions were at least 70% supervised, they seemed to be more effective for older adults' balance and strength outcomes than unsupervised exercise programs (Lacroix et al., 2017). A combination of 12-month, twice weekly, supervised, center-based exercise and up to four times a week of unsupervised home-based exercises decreased mobility disability among sedentary older adults (Pahor et al., 2014).

Transportation to the center at which the exercise is conducted may be a barrier to participation (Franco et al., 2015). To lower this barrier, a solution might be to exercise at home. Adherence has been higher to home-based programs for older adults, than to center-based exercise interventions (Ashworth et al., 2005) because no transportation is needed. A systematic review of a home-based exercise intervention for frail older adults concluded that it may decrease disability among older people with moderate frailty (Clegg et al., 2012). Since then, some more studies have reported results from frail older adults' home-based exercise programs, but results from supervised home-based programs are still scarce, as most home-based programs have been unsupervised. Table 1 summarizes previous home-based programs for frail older adults. The effects on physical performance of a 12-week home-based exercise program, with weekly contact with a physiotherapist through either a home visit or phone call, were not significant in comparison to usual care (Clegg et al., 2014). A 12-month intervention tailored according to the frailty characteristics met maintained physical performance measured using the Short Physical Performance Battery (SPPB), whereas the SPPB scores decreased in the usual care control group (Cameron et al., 2013). A six-month unsupervised exercise program with a few phone-calls and checkups increased handgrip and lower extremity strength in comparison to usual care (Hsieh et al., 2019). A combination of a 12-week, center-based, supervised exercise program followed by a 12-week unsupervised, home-based exercise program had an impact on balance and on Timed up-and-go test results in comparison to usual care (Sadjapong et al., 2020).

2.6.2 Other related methods

Alongside physical exercise, other options for managing frailty include addressing polypharmacy, malnutrition, and treatable causes of weight loss, and exhaustion (such as depression, anemia, hypotension, hypothyroidism, and B_{12} vitamin deficiency) (Dent et al., 2019). As frailty overlaps with multimorbidity, frail older adults often have polypharmacy, and checking the suitability of these people's medications may have an impact on the severity of their frailty (Gutiérrez-Valencia et al., 2018). Polypharmacy can be addressed using, for example, the Beers criteria, which helps the physician recognize possibly harmful drugs and drug combinations in older adults (By the American Geriatrics Society 2015).

Weight loss in frailty is linked to malnourishment and anorexia of aging (Landi et al., 2016; Merchant et al., 2022). As part of frailty management, it is important to intervene in possible malnutrition (Dent et al., 2017). The risks of malnutrition can be identified using, for example, the Mini Nutritional Assessment (Vellas et al., 2006). If protein intake is low (Lorenzo-López et al., 2017) and distributed unevenly throughout the day, the risk of developing frailty is higher (Bollwein et al., 2013). Low levels of energy intake, vitamins D, E, and folate are also associated with more severe frailty (Bartali et al., 2006). By paying attention to frail people's nutrition, it might be possible to prevent frailty advancing into disability (Artaza-Artabe et al., 2016).

Protein supplementation alone does not improve the strength, functioning, or muscle mass of frail older adults (Oktaviana et al., 2020). Exercise combined with protein supplementation was a more effective method for delaying or reverse frailty than health education, nutrition, home visits, hormone supplementations, or counseling (Travers et al., 2019). Multicomponent programs (combining e.g., exercise with nutrition or hormone therapy) seem to be more effective on frailty characteristics and physical functioning than programs utilizing only one component (e.g., only nutrition, or hormone therapy) or usual care (Dedeyne et al., 2017). Even though physical exercise seems to be effective for managing frailty (Apóstolo et al., 2018), whether exercise should be delivered in groups or one-to-one, and the optimal duration, frequency, and cost-effectiveness of interventions remains unclear (Apóstolo et al., 2018; de Labra et al., 2015; Dedeyne et al., 2017; Giné-Garriga et al., 2014; Travers et al., 2019).

TABLE 1 Summary of studies with home-based exercise interventions among frail older adults.

1st author, year, country	Frailty assessment	Duration	Intervention group	Control group	Functioning Outcomes
Clegg et al. 2014, UK	Frail according to Edmonton Frailty scale	12 weeks	Home-based exercise intervention (n=45) with weekly home visit by physiotherapist (5x) and checkup phone-calls (7x)	Usual care (n=39)	TUG, Barthel index
Cameron et al. 2013, Australia	Frail according to Frailty phenotype criteria	12 months	Intervention (n=120) tailored according to frailty criteria met. Weight loss criterion: dietitian-evaluated nutritional intake, home delivered meals, nutritional supplementation. Exhaustion criteria with depressive symptoms: participant was referred to psychiatrist or psychologist and encouraged to take part in activity groups and telephone contacts. Weakness, slowness, or low physical activity criteria: 10 home-based physiotherapy sessions and 12-month home-based unsupervised exercise program	Usual care (n= 121)	SPPB, Barthel index
Pahor et al. 2014, USA	Sedentary older adults assessed with frailty phenotype (not all frail)	2.6 years	Center-based supervised exercise 2x/week + 1 to 4 /week home-based exercise. After 52 weeks up to end of trial, unsupervised home-based exercise 3–4 x/ week	Health education group (=211)	400m walk, SPPB
Hsieh et al. 2019, Taiwan	Pre-frail or frail according to Frailty phenotype criteria	6 months	Exercise (n= 79): unsupervised home-based individualized strength, flexibility, balance, and endurance training 5–60min./3–7x/week with phone call checkups. Nutrition (n=83): counseling on proper nutrition and food supplements. Exercise & Nutrition (n=77): combination of previous.	Usual care (n=80)	Hand grip strength, gait speed, upper body flexibility, lower extremity strength
Sadjapong et al. 2020, Thailand	Frail according to Frailty phenotype criteria	24 weeks	Multicomponent exercise with 12 weeks of supervised center-based 3x/week followed by 12 weeks of unsupervised home-based exercises 3x/week (n=32)	Usual care (n=32)	Hand grip strength, BBS, TUG, VO_2 max

Note: TUG, Timed Up-and-Go test; SPPB, Short Physical Performance Battery; BBS, Borg Balance Scale; VO_2 Max, Maximal oxygen consumption.

3 AIMS OF THE STUDY

This study was part of the larger HIPFRA (HIP fracture and FRAilty) research project, which investigated the effects of a 12-month home-based, physiotherapist-supervised physical exercise intervention on days spent at home, utilization of social and health care services, functioning, and quality-of-life among home-dwelling older adults with signs of frailty or operated hip fractures. This thesis used the data on people with signs of frailty. Its specific aims and research questions are:

1. What are the effects of a 12-month supervised, home-based exercise intervention on days lived at home and the utilization of social and health care services over 24 months among older adults with signs of frailty (Publication II)?

2. What are the effects of a 12-month supervised, home-based exercise intervention on functioning (Publication III), quality of life (Publication II), and the severity of frailty (Publication IV) among older adults with signs of frailty?

3. Among older adults with signs of frailty, is a 12-month home-based, physical exercise program cost effective (Publication II)?

4. Does the severity of frailty affect the functional independence and quality of life of older adults (Publication I)?

4 MATERIALS AND METHODS

4.1 Study design

This thesis is based on data gathered from people with signs of frailty in a randomized controlled trial (RCT), HIPFRA (HIP fracture and FRAilty), between December 2014 and August 2018. The trial was conducted in the province of South Karelia (133,000 inhabitants), Finland. HIPFRA studied the effects of long-term, home-based, physiotherapist-supervised physical exercise intervention on two separate patient groups: a) people with recently operated hip fractures (n=121) and b) people with signs of frailty (n=300). The data from these two groups were analyzed and the results reported separately and according to intent to treat principle. Figure 4 presents the whole HIPFRA study design.

After baseline assessments, the participants with signs of frailty were allocated into either a home-based, physiotherapist-supervised, physical exercise group (n=150) or a usual care control group (n=150). To ensure even distribution into the groups, a computer-generated random sequence allocation program with randomly varying block sizes from 2 to 10 was used. The project manager of the HIPFRA study was the main user of the allocation program, which was generated by a statistician who did not participate in any way in the HIPFRA study.

Data were collected from both randomization groups through measurements and interviews at baseline and at three, six, and 12 months as well as by retrieving information from the South Karelia Social and Health Care District´s (Eksote) medical records and registers. Register information was gathered from all participants for 730 days after their individual randomization day. All the measurements and interviews were performed at the participants' homes between December 2014 and August 2017, and the register data were retrieved between December 2014 and August 2018.

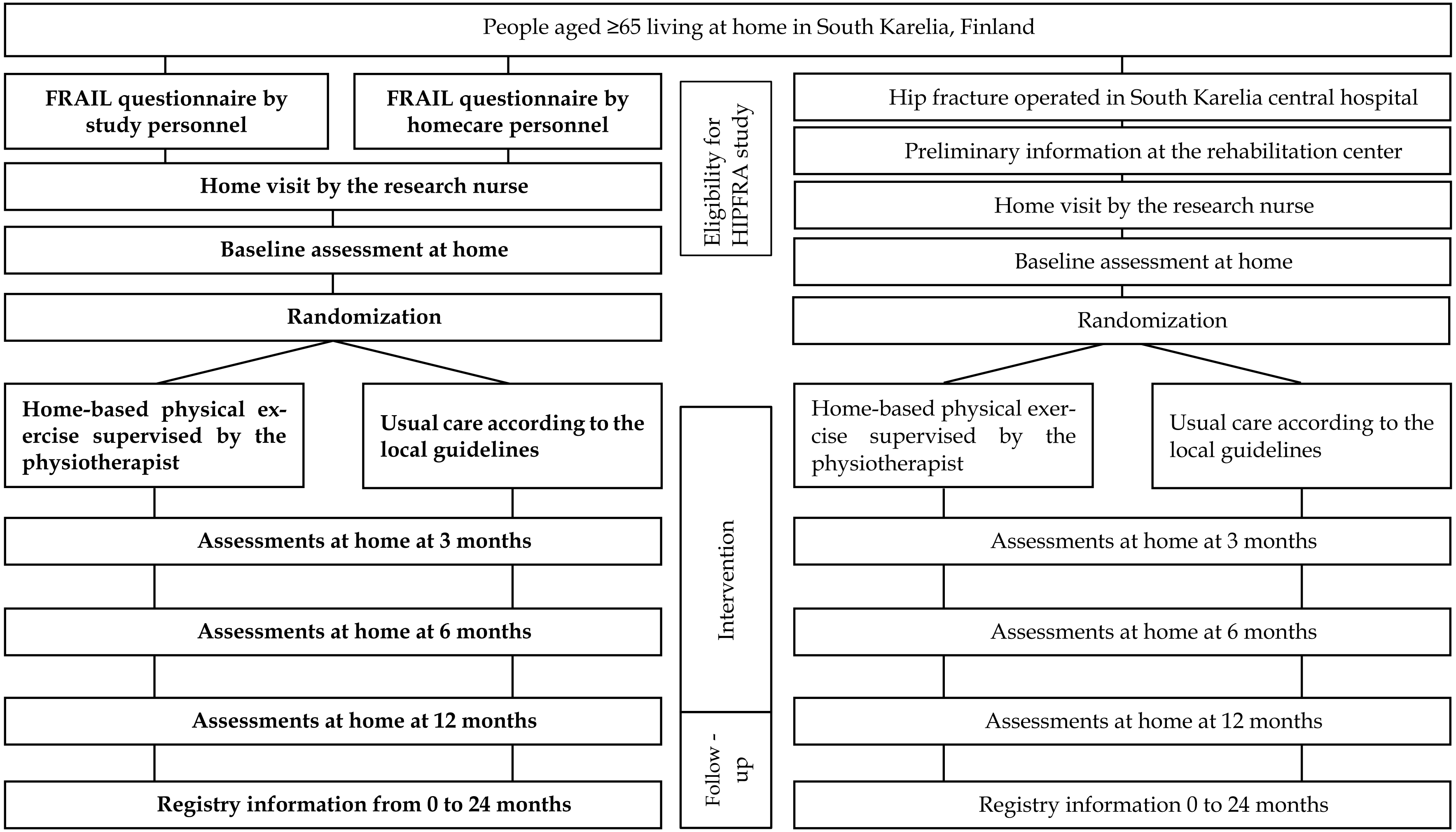

FIGURE 4 Study design of randomized controlled trial HIPFRA (HIP fracture and FRAilty). Study design for people with signs of frailty (left, bolded), and patients with operated hip fractures (right).

4.2 Participants

Participants were recruited via advertisements in local newspapers and with the help of the Eksote personnel (mainly in homecare). Inclusion criteria were age of 65 or older, living at home (homecare by health care personnel allowed), ability to walk about indoors (mobility aid allowed), ability to communicate in Finnish, a score of at least 17 points in the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), a score of at least one point in the FRAIL questionnaire (Fatigue, Resistance, Ambulation, Illness and Loss of weight, Table 2) (Abellan van Kan et al., 2008; Morley et al., 2012), and meeting at least one frailty phenotype criteria (Fried et al., 2001). A person was not eligible if they lived in a 24-hour care facility, had an illness that prevented them from participating in physical exercise (e.g., severe neurological, pulmonary, cardiorespiratory, musculoskeletal illness), terminal cancer, alcohol or drug abuse, or problems with hearing or eyesight that caused communication difficulties.

Preliminary eligibility was assessed using the FRAIL questionnaire (Table 2), (Abellan van Kan et al., 2008; Morley et al., 2012) which was translated into Finnish by the HIPFRA research group and can be found in Soukkio et al. (2020). The FRAIL questionnaire had five questions on fatigue, resistance, ambulation, illnesses, and loss of weight, and each one scored either one or zero points. A person was eligible for the next phase of the HIPFRA study recruitment if they had a sum score of one or two (pre-frail), or a score of three to five (frail). If a person scored zero points, they were excluded, as this meant they had no signs of frailty. The FRAIL questionnaire was performed over the phone if a person contacted the research personnel after seeing the advertisement in the newspaper. If homecare personnel recruited a person, they conducted the preliminary screening for FRAIL and send it to HIPFRA´s project manager

In the next phase of recruitment, the research nurse visited the person's home and verified their eligibility and frailty status using the five frailty phenotype criteria (Fried et al., 2001). If the person met one or two (pre-frail) or, three to five (frail) of the five criteria, the person was considered eligible for the HIPFRA study. A detailed description of the frailty phenotype criteria used in this study is presented in Section 4.4.7. If the person was eligible and willing to participate, the baseline assessment visit was scheduled.

TABLE 2 FRAIL questionnaire (Abellan van Kan et al., 2008; Morley et al., 2012).

FRAIL	Question	Answer alternatives	Points
Fatigue	How much of the time during the past 4 weeks did you feel tired?	All of the time Most of the time Some of the time A little of time or none of the time	1 1 0 0
Resistance	By yourself and not using aids do you have any difficulty walking up 10 steps without resting?	Yes No	1 0
Ambulation	By yourself and not using aids, do you have any difficulty walking several hundred yards (300 meters)?	Yes No	1 0
Illnesses	Did a doctor ever tell you that you have (illness)? The illnesses include the following: hypertension, diabetes, cancer (other than minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, kidney disease	A person has 5–11 of the listed illnesses A person has 0–4 of the listed illnesses	1 0
Loss of weight	How much do you weigh now with your clothes on but without shoes and how much did you weigh a year ago?	>5% weight loss during the previous year <5% or no weight loss during the previous year	1 0

4.3 Ethics

In the planning phase, at the end of February 2013, the HIPFRA study received preliminary ethical approval from the Eksote´s ethics committee. The finalized study plan was approved by the coordinating ethics committee of the Helsinki University Hospital in November 2014. At the beginning of December 2014, HIPFRA was registered on an international clinical trial database, clinicaltrials.gov, register number NCT02305433. After receiving ethical approval and completing the trial registration at the beginning of December 2014, HIPFRA received permission from Eksote to begin recruiting participants.

During the home visits, the research nurse gave oral and written information on the study and answered all questions concerning participation. All the participants signed a written consent document before the baseline assessments. By signing, the participants granted the researchers permission to access their medical records for data collection and to use the collected data in the study.

All the participants were volunteers and had the right to withdraw from the study at any point. All the collected data were pseudonymized and retained according to the personal data protection law. The assessors, who conducted the home visits, and the physiotherapist, who supervised the exercise intervention at the participants homes were trained to ensure the safety and privacy protection of the participants and themselves. They were also trained to give first aid, if needed. Potential adverse effects were screened throughout the study.

4.4 Measurements and data collection

The primary outcome of the HIPFRA study was days lived at home over the 24 months. Secondary outcomes consisted of the utilization and costs of social and health care services (24 months), QOL (12 months), functioning outcomes of physical performance and functional independence (12 months), and the severity of frailty (12 months). Assessments at the participants' homes were conducted by the research physiotherapist or a research nurse, who were not blinded for group allocation, and did not participate in the allocation process or the implementation of the intervention. One assessment visit lasted approximately 1.5 hours. Register data were retrieved from the medical records by the Business Intelligence (BI) analyst, who was blinded for the allocation.

4.4.1 Days lived at home

The number of days lived at home over 24 months were calculated by deducting the number of the participant's overnight stays in hospital acute wards, in long-term wards, in 24-hour care facilities (e.g., nursing homes), and the number of days after death, from the maximum of 730 days. The BI analyst collected all the information on the length of stays in wards, 24-hour care facilities and dates of death from the participant's electric medical records held by the local social and health care service provider, Eksote. The outcome was reported as the number of days, with 95% confidence intervals.

4.4.2 Survival

The survival percentage was calculated over 24 months for both groups from the date of death. The information on the day of death was retrieved from Eksote's medical records.

4.4.3 Utilization of social and health care services

The BI analyst also gathered information on the utilization of social and health care services from the local social and health care provider´s (Eksote), register and medical records. In Finland, local municipalities or joint municipalities are responsible for organizing health care and social services for its residents. Health care services include primary and secondary specialized medical care. Primary care is provided at municipalities' health centers and includes prevention, monitoring, diagnosis, and treatment of diseases. Specialized medical care from medical or dental specialists includes secondary health care in central hospitals and tertiary health care mainly at university hospitals. Social services include services to meet older adults' support needs, for example, home services (assistance in showering, and other daily living activities), support for informal caregivers, services to support mobility, and institutional care. All communication between the patient and social and health care service professionals must be documented in their medical records. As Eksote is primarily responsible for all the public health care and social services provided in the area of South Karelia, Eksote's medical records and registers cover all primary health care, specialized medical care, and social care.

For utilization of health care services, the number of in-patient stays at wards (acute and long-term), and all face-to-face contacts and phone consultations between health care professional (e.g., physicians, nurses, physiotherapists, occupational therapists) and the participants were included. Social care included temporary and permanent stays in nursing homes and other 24-hour care facilities for older adults. If the participant was referred to health care services at Helsinki University Hospital or in some other hospital district in Finland, the information on the outpatient visits and inpatient days were retrieved through payments for Eksote services.

In addition to the information retrieved from public health care and social services, the utilization of private health care and rehabilitation services were retrieved from the Social Insurance Institution of Finland's (Kela) registers. Private health care and rehabilitation are covered by Kela's register if the patient has applied for compensation, to which they are entitled by Finnish law. Private practice health care contacts were added to the gathered information on public health care.

4.4.4 Costs of social and health care services

The costs of social and health care services were calculated from the health care provider's perspective from the data of service utilization collected from Eksote´s registers. The costs (EUR) were calculated and reported per person-year. The national mean unit costs from 2011 (Kapiainen et al., 2014) were corrected to the level of 2018, according to the inflation rate and cost-of-living index. The mean unit cost was then multiplied by the number of contacts (e.g., with a physician, nurse, physiotherapist, occupational therapist), visits (e.g., by homecare personnel), or in-patient days (e.g., overnight stays at wards). The costs of the physical exercise intervention were included in the total costs of rehabilitation. A mean cost of EUR 86.50 per one physiotherapist intervention visit was used.

4.4.5 Quality of life

QOL was assessed using the 15-dimensional (15D) questionnaire (Sintonen, 2001), which contains 15 questions, each with five answer options. The 15 domains are mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental functions, discomfort and symptoms, depression, distress, vitality, and sexual activity. A QOL index is calculated from the questionnaire responses. The index can range between 0 and 1, where zero means death and 1 the best possible quality of life.

At baseline, the research nurse gave the 15D questionnaire to the participant during the recruitment visit. The filled-out questionnaire was collected during the baseline assessments. At three, six and 12 months, the questionnaire was mailed to the participant a few weeks before the assessment visit and then collected during the visit. If the participant could not answer the questionnaire by themselves, their next of kin or some other close person helped them. If the participant had no-one to help, the assessor helped them fill out the questionnaire during the assessment visit.

4.4.6 Functioning

Functioning measurements included physical performance, functional independence in ADL, IADL, leisure-time physical activity and number of falls. Assessments were performed at baseline, three, six and 12 months at the participant's home by the trained research physiotherapist or research nurse in accordance with the study protocol.

The Short Physical Performance Battery (SPPB) consists of three components: balance, walking speed and the chair-rise test (Guralnik et al., 1994). All components have scores from zero to four (Table 3), with a maximum total score of 12. Balance was tested in three stances (parallel, semi-tandem and tandem) with a maximum time of 10 seconds each. If the person could hold the stance for a full 10 seconds, they moved on to try the next stance. Walking speed was mainly tested with a 4 m walk. If space at home was limited, 2.44 m was used instead. Participants were instructed to walk at their normal pace, and a walking aid was allowed if they normally used one. In the chair-rise test a kitchen chair (or chair with similar height) was used. Participants were instructed to rise five times as fast as possible; arms crossed in front of their chests, and in an upward position, to fully extend their hips and knees, then sit down, touching the back of the chair with their back.

TABLE 3 Short Physical Performance Battery (SPPB) scoring of three components (Guralnik et al., 1994, 2000).

Points	Balance	Walking 4m (s)	Walking 2.44m (s)	Chair rise 5x (s)
4	Able to stand 10s in all three stances	<4.82	<3.2	<11.19 s
3	Able to stand 10s in parallel and semi tandem, 3.0–9.99s in tandem	4.82–6.20	3.2–4.0	11.20–13.69
2	Able to stand 10s in parallel and semi tandem stance, <3.0s in tandem	6.21–8.70	4.1–5.6	13.70–16.69
1	Able to stand 10s in parallel stance, <10s in semi-tandem	>8.70	>5.6	>16.7
0	Unable to stay in parallel stand for 10s	unable to walk	unable to walk	over 60s or unable to perform correctly

Handgrip strength was measured by a handheld Saehan dynamometer (Saehan Sh5001, Masan, South Korea). Measurement was taken in a seated position, shoulders in a neutral position, elbow unsupported at a 90-degree angle, wrists in a neutral position, thumbs facing upwards (Roberts et al., 2011). Handle position three was most often used for men and position two for women and men with small hands. The assessor encouraged the participant during the measurements. Handgrip strength was tested three times for each hand and the combined mean of the best values from both hands was used in the analyses. The calibration of the dynamometers were checked monthly with 10kg and 20kg weights.

The Functional Independence Measure (FIM) (Granger et al., 1986) was used to assess the amount of assistance the person might need in 18 daily tasks and was assessed by interviewing the participant. The FIM consists of 13 motor and five cognitive tasks, which are evaluated on a scale from seven (fully independent) to one (unable to perform and needs two-person assistance) and has a maximum of 126 points (motor subscale 91 and cognition subscale 35 points). The motor subscale includes tasks such as eating, showering, getting dressed, getting in/out of bed, and walking stairs. The cognition subscale includes tasks of understanding, speaking, remembering, social behavior, and problem solving.

Instrumental Activities of Daily Living (IADL) were assessed using the IADL questionnaire (Lawton & Brody, 1969). The assessor interviewed the participant about their ability to perform instrumental activities such as laundry, shopping groceries, and taking care of medication, using the questions in the IADL questionnaire. The IADL total score was calculated using a polytomous item sum, in which individual tasks were scored from 1 to 3, 4, or 5, the total sum ranging from 8 to 31 (Vittengl et al., 2006). A higher score indicated better ability to perform IADL tasks.

Leisure-time physical activity (outside the intervention) was assessed by two questions (Helldán & Helakorpi, 2014): 1) How often did you have a walk outdoors for at least 30 minutes at a time in the previous month? and 2) how often did you perform physical activities other than walking for at least 30 minutes at a time in the previous month? Physical activity sessions from both questions were summed up and reported as number of weekly sessions. The exercise sessions of the intervention were not included.

Number of **falls** were elicited in the interview during the assessment visits. The participants were asked "Did you have any falls during the previous three/six months". The time period was three months at the baseline, three-, and six-month assessments, and six months at the 12-month assessment visit. If the person had fallen, the number of falls and possible injuries related to the fall were elicited. The number of falls during the year was summed up and reported as the number of falls per person-year.

4.4.7 Severity of frailty

The research nurse or research physiotherapist assessed the severity of frailty with slightly modified frailty phenotype criteria (Fried et al., 2001) at baseline and at 12 months. The participant was classified as pre-frail or frail according to the number of criteria they met; pre-frail if they met one or two of the five criteria, frail if they met three or more. If at 12 months they did not meet any, they were classified as non-frail. The five frailty phenotype criteria used in the study were:

1. The unintentional weight loss criterion was met if the person had unintentionally lost more than 5% of their weight when their current weight was compared to the previous year´s weight (Fried et al., 2001). Weight was measured on an Omron HN289 scale (Kyoto, Japan). The previous year´s weight was elicited from the participant at baseline and checked in medical records, if possible.

2. The low physical activity criterion was assessed by asking "How often did you do some physical activities such as walking, calisthenics, dancing etc.?". The person met the criterion if they answered that they had been physically active less than once a week for 30 minutes. The question was based on the Falls Risk for Older People in the community (FROP-Com) questionnaire (Russell et al., 2008), which has been validated for older adults.

3. The exhaustion criterion consisted of two questions: a) "How often during the past week did you feel, that you could not get going?" and b) "How often during the past week did you feel that everything you did was an effort?" The criterion was met if the person answered "most of the time" or "all of the time" to either of the two questions (Fried et al., 2001). The questions are from the Center of Epidemiology Studies Depression scale (CES-D) (Orme et al., 1986).

4. The weakness criterion was met if the person had hand grip strength under the cutoff value, defined by BMI and sex. Hand grip was measured using a Saehan (Sh5001, Masan, South Korea) dynamometer. The original cutoff from Fried et al. (2001) was used.

Women		Men	
BMI (kg/m2)	Cutoff (kg)	BMI (kg/m2)	Cutoff (kg)
≤26.0	≤17	≤24.0	≤29
26.1–29.0	≤18	24.1–28.0	≤30
>29.0	≤21	>28.0	≤32

5. Slowness was assessed with a 4 m walk. A mobility aid was allowed if the participant usually used one. They were asked to walk at their normal speed and the best of two attempts was recorded. If the time taken to walk four meters was over 8.7 seconds, the person met the criterion. If their home did not allow a 4 m walk, a shorter distance (2.44 meters) was used. In the 2.44-meter walk the cutoff time was 5.2 seconds. Both cutoffs were based on the lowest fourth of the walking test in SPPB (Guralnik et al., 1994).

4.5 Intervention

4.5.1 Home-based physical exercise

The 12-month physical exercise intervention in the HIPFRA study consisted of home-based, physiotherapist-supervised, multicomponent exercise sessions of 60 minutes, twice a week. All the participants were assigned a personal physiotherapist who came to their home and conducted all the exercise sessions for the whole 12 months. The participants were allowed two weeks off during the exercise intervention. They were free to use any social or health care services they needed during the intervention (12 months) and follow-up (12 months). In total, 24 physiotherapists from seven local private physiotherapy companies were selected on the basis of tendering to implement the intervention. The selected physiotherapists had to have at least two years of professional work experience as a physiotherapist and additional training or experience in physiotherapy for older adults.

The basic structure of one exercise session (60 minutes) contained six components: warm-up (5–10 min), resistance training (30–40 min), balance training (5–10 min), flexibility training (5–10 min), functional exercises (5–10 min), and brief counseling on nutrition and physical activity. The basic structure of the progressive multicomponent exercise program was designed by the research group. Before the intervention started, all 24 physiotherapists were trained to conduct to the home-based physical exercise intervention, its basic structure and contents, progression, and targeted intensities. The physiotherapists were allowed to tailor the contents of the sessions to match the participants' fitness and health status and individual goals. Individual goals for the participants were set using the Goal Attainment Scale (GAS) method (Kiresuk & Sherman, 1968; Turner-Stokes, 2009) in cooperation between the physiotherapist and the participant.

Every session began with a warm-up of five to ten minutes, to prepare the body for the upcoming exercises. This could be walking, chair exercises, stationary cycling, or exercise using other fitness equipment that the participant owned. Intensity was from low to moderate.

The main emphasis of the exercise session was on resistance training, which lasted for 30 to 40 minutes. This training was progressive and was divided into strength, power, and endurance periods, lasting approximately eight weeks, and were rotated throughout the year. The main exercises were based on the strengthening exercises of the Otago exercise program (Gardner et al., 2001), which are knee extension, knee flexion, hip abduction, ankle plantarflexion (up to toes), and ankle dorsiflexion (back on heels). These were performed in almost every exercise session. Resistance was added with ankle weights (from 0.5 to 10 kg), dumbbells, kettlebells, and weight vests. Sets and repetitions were alternated according to the phase of the resistance cycle and the participant's fitness level. The strength training period consisted of sets of 2 to 5, repetitions of 8 to 12, with a resistance of 60–80% of maximum muscle strength. Power training included sets of 3–5, repetitions of 4 to 10, with a resistance of 20–60% of maximal strength. Endurance training included sets of 2 to 3, repetitions of 12 to 30, with resistance of 20–60% of maximum strength. The suitable amount of resistance was evaluated using a multiple repetition maximum (RM) test mainly performed for knee extension with ankle weights (Avers & Brown, 2009). The intensity of the exercises was from moderate to vigorous. Intensity was monitored using Borg´s (1982) Ratings of Perceived Exertion (RPE) after every session, and the next session was modified accordingly. In addition to lower limb exercises, upper limb exercises were also performed, although they were not specifically assigned.

Flexibility training often took place in connection with other components such as warm-up and functional exercises. The goal was to enlarge the range of motion (ROM) in the large joints to maintain the ability to perform ADL. The exercises involved mainly stretching and reaching.

Balance training lasted for five to ten minutes. It included static, dynamic, and dual-task exercises, alternating surfaces, and balance pads to challenge the participant's sense of balance.

Functional exercises were used to practice key IADL, which are needed for maintaining functional independence and the ability to continue living at home. The exercises were customized to suit the participants' goals, needs and environment and they combined resistance, balance, and flexibility exercise elements. The tasks included washing dishes, lifting dishes into cupboards, hanging out laundry, walking stairs, making and piling firewood, and walking to the grocery store.

During the exercise session, the physiotherapist gave brief counseling on nutrition and leisure-time physical activity. The goal of the nutrition counseling was to inform the participants of national nutritional guidelines and encourage them to get enough protein to support the resistance training. The physiotherapist was aware of the results of the participant's Mini Nutritional Assessment (MNA) (Vellas et al., 2006) so they could tailor the counseling to the participant's needs. The physical activity counseling mainly consisted of encouraging and motivating the participants to be physically active in their day-to-day lives, to meet the national physical activity guidelines.

The physiotherapists kept logs of the sessions' contents (exercise type, sets, repetitions, resistance equipment used and its weight/size), ratings of perceived exertion (RPE) (Borg, 1982), counseling given on nutrition or physical activity, and possible adverse effects. They sent the logs monthly to the research group.

4.5.2 Usual care

The participants in the usual care (control) group continued to live their lives as usual. They were allowed to use any social and health care services they needed during the 24 months. They could also receive rehabilitation if they needed, in accordance with the social and health care district's policies.

4.6 Statistical methods

The primary outcome of the HIPFRA study was the number of days lived at home over 24 months. No previous research data were available on how long the people with signs of frailty had lived at home for the statistical power calculations. The sample size calculations were based on the data from the PERFECT (PERFormance, Effectiveness and Cost of Treatment episodes) study (Sund et al., 2011) of Finnish patients with hip fractures, which offered data on the proportion of patients living at home one year after the fracture. To detect the hypothesized difference (α=0.05, power=80%) of 180 days between the exercise and usual care groups, a sample size of 91 people was required in each group. To allow for discontinuation (estimated as 15%) and death (20%) of participants during the 24 months, our targeted sample size was 300 participants. The same targeted sample size was used for people with signs of frailty and patients with hip fractures in the HIPFRA study.

Statistical analyses were performed using the Stata 17.0, StataCorp LP (College Station, TX, USA) statistical package. The characteristics of the participants are reported as means with standard deviations (SDs) or as counts with percentages (%). The number of days lived at home (primary outcome) and utilization of social and health care services were analyzed using Poisson's model and reported as number of days or visits per person-year and incidence rate ratios (IRRs) with 95% confidence intervals (CIs). The survival curve was plotted using the Kaplan–Meier method and the log-rank test for assessing the significance of the differences between the randomization groups in terms of survival.

Costs were analyzed using a generalized linear regression model with log link and gamma variance functions. The variance function was selected on the basis of Park's test and Akaike's information criterion. All costs (EUR) were presented per person-year. The QALYs were based on the areas under the curve of the 15D scores from baseline to the last measurement point, and all participants who completed the baseline assessment and had at least one of the three measurements (at 3, 6, or 12 months), were included in the analyses. The ICER was calculated from the costs and QALYs over 12 months. The bootstrapping technique (5000 replicates) was used in connection with the ICER planes for costs and QALYs. The normality of the variables was evaluated graphically, using the Shapiro–Wilk W test.

Repeated measures of secondary outcomes (functioning and quality of life) were analyzed using mixed-effects models with unstructured covariance (Kenward–Roger method to calculate degrees of freedom). The fixed effects were group, time, and group–time interaction. The normality of the variables was tested using the Shapiro–Wilk W test.

5 RESULTS

5.1 Baseline characteristics of participants (Publication I)

Three hundred people were eligible and were randomized. A total of 299 participants were included in the analyses (Figure 5), as one participant from the usual care group withdrew and refused to allow the use of their collected baseline data in the analyses. Table 4 describes the participants' baseline characteristics.

TABLE 4 Baseline characteristics of exercise and usual care groups with mean and standard deviation (SD) or frequency with percentage (%).

Characteristic	**Exercise (n=150)**	**Usual care (n=149)**
Age, mean (SD)	82.2 (6.3)	82.7 (6.3)
Female, n (%)	114 (76)	110 (74)
Lives alone, n (%)	88 (59)	86 (56)
Body Mass Index (BMI), kg/m^2, mean (SD)	28.4 (5.5)	28.6 (6.1)
Walking aid, n (%)	122 (81)	117 (79)
Mini-Mental State Examination (MMSE), mean (SD)	24.2 (3.1)	24.6 (3.2)
Number of regular prescription medications, mean (SD)	6.7 (3.2)	7.0 (3.1)
Physician-diagnosed disease or disorder, n (%)		
Alzheimer or other dementia	19 (13)	22 (15)
Cardiovascular disease*	76 (52)	91 (61)
Depression	25 (17)	25 (17)
Diabetes	31 (21)	45 (30)
Hypertension	110 (73)	110 (74)
Musculoskeletal disease	129 (86)	124 (83)
Osteoporosis	42 (28)	35 (24)
Urinary incontinence	95 (63)	96 (64)
Homecare at least once a week, n (%)	27 (18)	34 (23)
Meal delivery at least 3 times a week, n (%)	31 (21)	30 (20)

*coronary heart disease, angina pectoris, myocardial infraction, heart failure

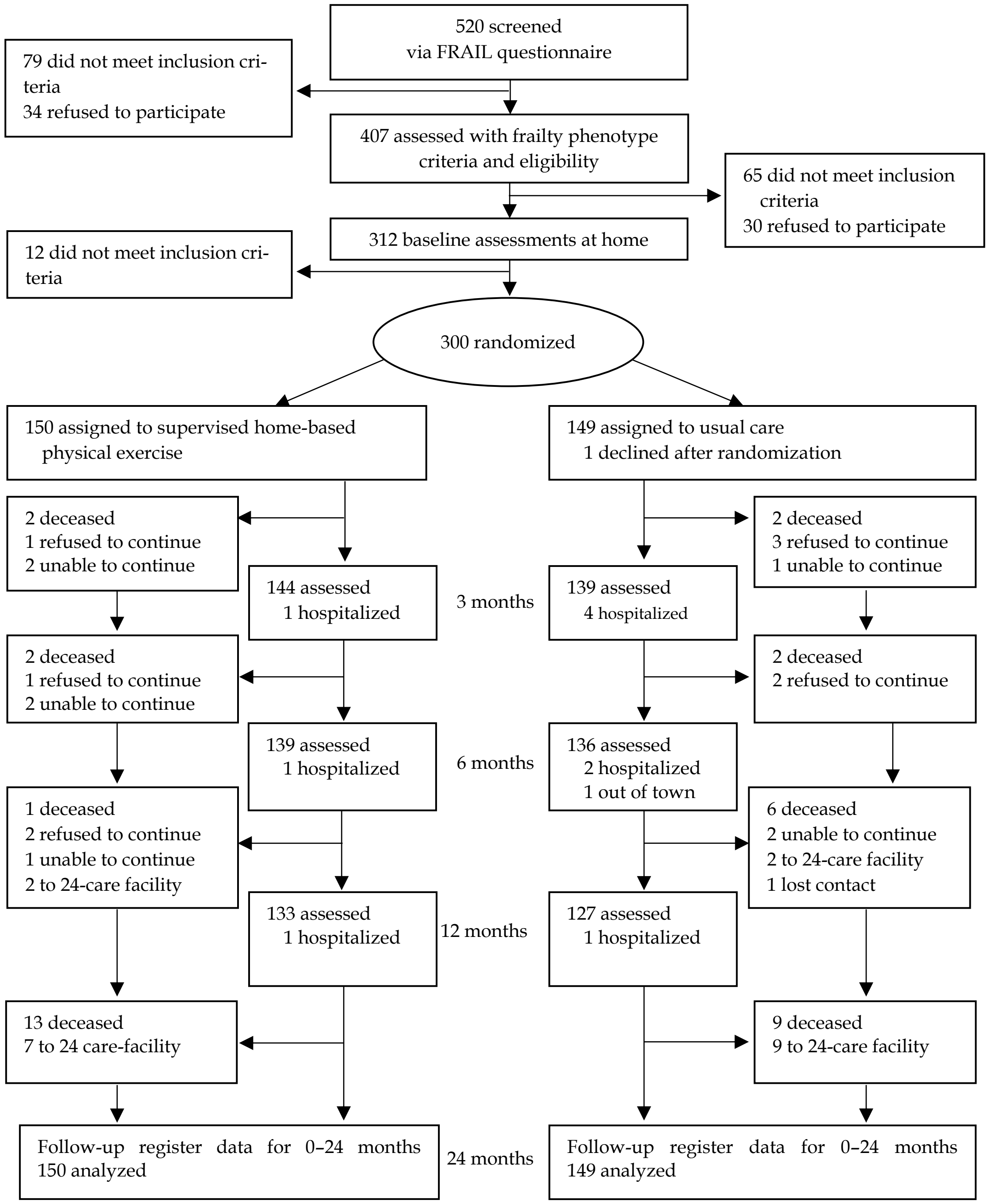

FIGURE 5 Flowchart of study with numbers of participants.

5.2 Adherence and adverse effects of home-based exercise

During the 12-month intervention period, 150 participants in the exercise group took part in a total of 12 981 home-based supervised exercise sessions, which is 87% of the total number of prescribed sessions. The median number of sessions for participants was 96 (IQR 87, 99), ranging from 3 to 104. The number of people who participated in at least 75% of the possible 104 exercise sessions was 128 (85%), and 134 participants took part in exercise sessions throughout the whole 12 months.

Sixty participants suspended the exercise program for two or more consecutive weeks. The reasons for temporary suspensions were acute hospitalization (e.g., acute infections, worsening of cardiac failure) or personal reasons (e.g., vacation, illness/death of family member). The longest temporary suspension was 10 weeks. After temporal suspension, 16 participants were unable to continue exercising due to medical reasons (n=9), being transferred to a 24-hour care facility (n=3), or death (n=4).

In the exercise group, 87 (58%) of the participants reported mild and transient exercise-related muscle soreness, and 106 (71%) reported mild joint pain, mainly in the knees and hips. Most often, the joint pain was associated with existing arthritis. During the exercise sessions, 17 falls occurred, one of which needed medical care, but the injury was not serious (knee pain). During or after some exercise sessions, 18 participants took extra nitroglycerin medication. Five participants needed acute medical care, when the physiotherapist arrived and found them to be unwell.

5.3 Days lived at home, and utilization and costs of social and health care services (Publication II)

5.3.1 Days lived at home over 24 months

Over 24 months (730 days) the participants in the exercise group lived at home for 659 (95% CI: 635 to 683) days, and those in the usual care 638 (95% CI: 611 to 665) days, IRR 1.03 (95% CI: 0.98 to 1.09). The days after death, overnight stays in 24-hour care facilities, long-term and acute wards decreased the number of days lived at home (Figure 6). The difference between the days lived at home in the two groups was not significant (p=0.26). There was also no difference between the groups (p=0.66) in terms of permanent placements into the 24-hour care facilities, as 11 people (7%) from the exercise group and 13 (9%) from the usual care group were placed in a 24-hour care facility.

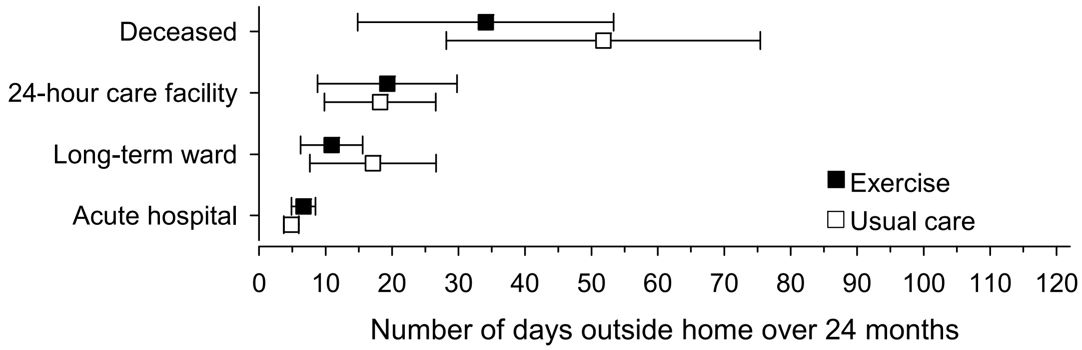

FIGURE 6 Mean number of days spent away from home by categories: days in acute hospital, in long-term wards, in 24-hour care facilities, and death. Mean number of days with 95% confidence interval whiskers.

5.3.2 Survival

The survival rates of the exercise and usual care groups did not differ over the 24 months (p=0.79) (Figure 7). In the exercise group, the 24-month survival rate was 88% (95% CI: 82 to 92), as over the 24 months, 18 people died, five of whom died during the first 12 months. In the usual care group, the survival rate was 87% (95% CI: 81 to 92), as 19 participants died during the 24 months, 10 of whom died during the first 12 months.

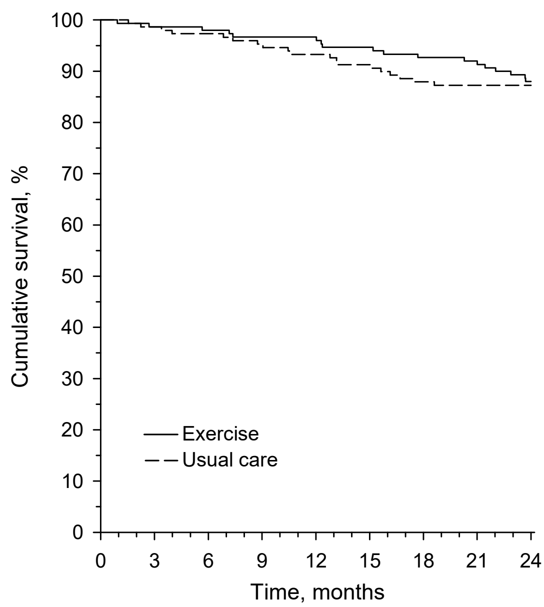

FIGURE 7 Cumulative survival rate (Kaplan-Meier) of participants in exercise and usual care groups over 24 months.

5.3.3 Utilization and costs of social and health care services

The utilization and costs of social and health care services were analyzed by different service categories over 12 months and 24 months. Over the first 12 months, the total costs of social and health care services per person-year were EUR 33,839 (SE 2167) in the exercise group and EUR 21,151 (SE 2185) in the usual care group, IRR 1.60 (95% CI: 1.23 to 1.98). The total social and health care service costs over 24 months in the exercise group were EUR 29,428 (SE 2282) per person-year, which was 1.23 times (95% CI: 0.95 to 1.50) higher than those in the usual care group, which were EUR 23,961 (SE 2198) per person-year.

At both time points, rehabilitation, which included the exercise intervention, was the only factor that significantly differed in the exercise and usual care groups. The physical exercise intervention increased rehabilitation costs by 5.79 times (95% CI: 4.28 to 7.30) more in the exercise group (EUR 8153, SE 145) than in the usual care group (EUR 1407, SE 187). Rehabilitation received outside of the intervention as part of usual care could include physiotherapy or occupational therapy, and the median number of standard care rehabilitation sessions received per person-year was 0 (IQR 0, 2) in the exercise group, and 1 (IQR 0, 8) in the usual care group.

Total costs were also analyzed in the subgroups according to baseline frailty severity. The pre-frail subgroup consisted of 91 participants in the exercise group and 91 in the usual care group. The total costs over 24 months were 1.46 times more in the exercise pre-frail subgroup (EUR 27,431, SE 3348) than in the usual care pre-frail subgroup (EUR 18,851, SE 2301) (Table 5). The rehabilitation costs in the exercise pre-frail subgroup were 5.22 times (95% CI: 3.93 to 7.01) more and the costs for visits to the emergency department were 1.71 times (95% CI: 1.03 to 2.89) more than those in the usual care pre-frail subgroup.

The frail subgroups had 59 participants in the exercise group and 58 in the usual care group. The total costs per person-year over 24 months, including intervention costs, were EUR 32,507 (SE 3625) in the exercise and EUR 31,979 (SE 3597) in the usual care group, IRR 1.02 (95% CI: 0.75 to 1.38) (Table 6). Two service categories differed significantly in the frail subgroups over the 24 months: the costs of inpatient days in primary health care wards (exercise EUR 1404 (SE 487) vs. usual care EUR 4365 (SE 1198), relative mean ratio (RR) 0.32 (95% CI: 0.12 to 0.73)) and rehabilitation (exercise EUR 4692 (SE 206) vs. usual care EUR 1958 (SE 307), RR 2.40 (95% CI: 1.77 to 3.34)).

TABLE 5 Costs over 24 months per person-year mean (SE) of social and health care service in exercise and usual care groups, by their pre-frail subgroups and relative mean ratio (RR) with 95% confidence intervals (CI). (Unpublished)

Social and health care service	Exercise (n=91) €/person year Mean (SE)	Usual care (n=91) €/person year Mean (SE)	RR (95% CI)
Home care, visits	3706 (807)	5222 (1122)	0.71 (0.38 to 1.32)
Primary care			
General practitioner, visits	1185 (153)	1342 (119)	0.88 (0.65 to 1.20)
Nurse, visits	958 (86)	1122 (97)	0.85 (0.68 to 1.11)
Rehabilitation*, visits	4950 (219)	948 (136)	5.22 (3.93 to 7.01)
Wards, days	3837 (1122)	2749 (1132)	1.40 (0.52 to 4.22)
Home health care, visits	330 (57)	436 (75)	0.76 (0.49 to 1.21)
Specialized medical care			
Physician, visits	713 (94)	678 (86)	1.05 (0.74 to 1.52)
Nurse, visits	70 (14)	64 (14)	1.09 (0.59 to 1.92)
Emergency department, visits	772 (168)	451 (74)	1.71 (1.03 to 2.89)
Hospital wards, days	5466 (1647)	3814 (1157)	1.43 (0.58 to 3.08)
24-hour care facility, days	623 (250)	1093 (460)	0.57 (0.12 to 2.43)

*includes trial intervention´s physiotherapist home visits, physiotherapy, occupational therapy, speech therapy

TABLE 6 Costs over 24 months per person-year mean (SE) by social and health care service in exercise and usual care groups, by their frail subgroups and relative mean ratio (RR) with 95 confidence intervals (CI). (Unpublished)

Social and health care service	Exercise (n=59) €/person year Mean (SE)	Usual care (n=58) €/person year Mean (SE)	RR (95% CI)
Home care, visits	10747 (2111)	13048 (2287)	0.82 (0.47 to 1.37)
Primary care			
General practitioner, visits	1450 (164)	1456 (220)	1.00 (0.70 to 1.44)
Nurse, visits	971 (126)	980(143)	0.99 (0.69 to 1.54)
Rehabilitation*, visits	4692 (206)	1958 (307)	2.40 (1.77 to 3.34)
Wards, days	1404 (487)	4365 (1198)	0.32 (0.12 to 0.73)
Home health care, visits	576 (137)	344 (82)	1.68 (0.85 to 3.04)
Specialized medical care			
Physician, visits	696 (130)	655 (100)	1.06 (0.62 to 1.66)
Nurse, visits	101 (37)	81 (23)	1.25 (0.49 to 3.17)
Emergency department, visits	650 (128)	777 (140)	0.84 (0.48 to 1.48)
Hospital wards, days	4446 (1392)	4180 (1076)	1.06 (0.50 to 2.38)
24-hour care facility, days	2191 (1018)	2279 (934)	0.96 (0.20 to 4.08)

*includes trial intervention´s physiotherapist home visits, physiotherapy, occupational therapy, speech therapy

5.3.4 Cost-effectiveness

The exercise group gained 0.040 QALYs more than the usual care group over the 12 months, and their total social and health care service costs were significantly higher. This means that all the participants were in the northeast quadrant (Figure 8) of the ICER plane, implying that exercise was more effective but more expensive than usual care.

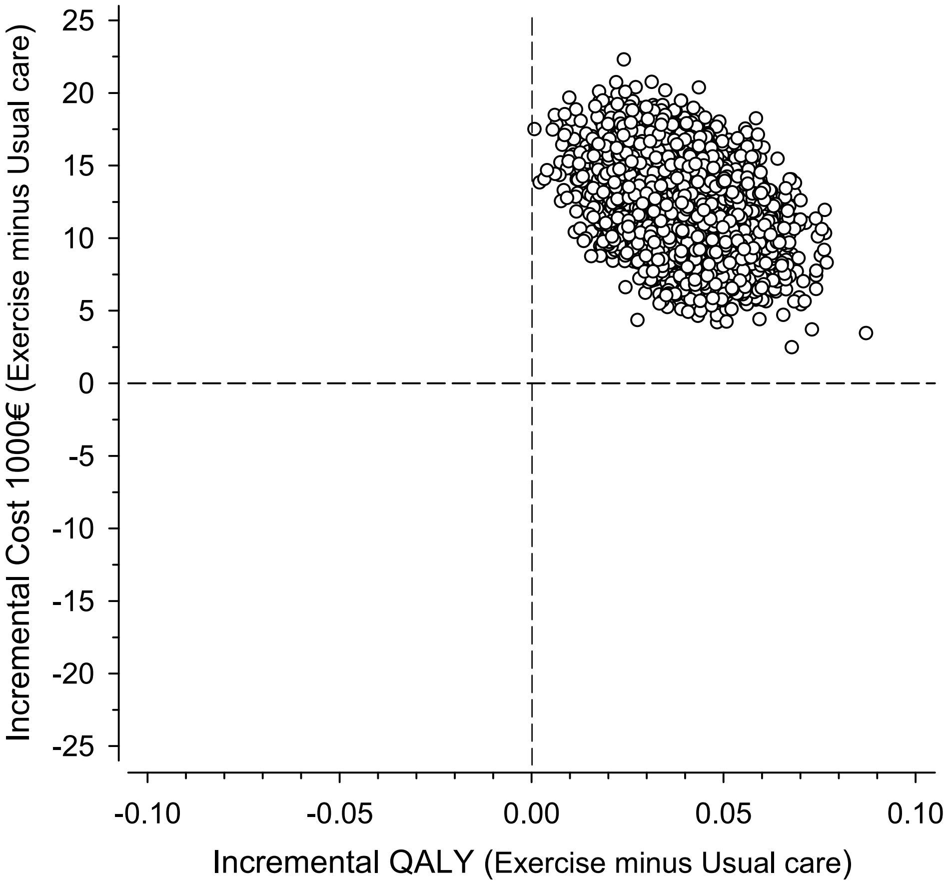

FIGURE 8 Incremental cost-effectiveness (ICER) plane for costs (€) and quality-adjusted life-years (QALY) of 5000 bootstrapped replicants.

5.4 Quality of life (Publication II)

At baseline, QOL was inversely associated with the severity of frailty. The participants who met only one frailty criteria had a higher mean QOL than those who met multiple criteria (Table 7). At baseline, the mean 15D index was 0.719 (SD 0.084) in the exercise group. The score did not change during the intervention year and at 12 months, it was 0.723 (SD 0.087, 95% CI: 0.709 to 0.738). In the usual care groups, the baseline score was 0.705 (SD 0.097), and decreased to 0.683 (SD 0.103, 95% CI: 0.667 to 0.700) over the 12-month period.

Of the single dimensions of the 15D, in the exercise group only sleeping increased significantly from baseline to 12 months. In the usual care group eight dimensions (vision, hearing, breathing, eating, usual activities, depression, and vitality) decreased significantly over the 12 months (Figure 9).

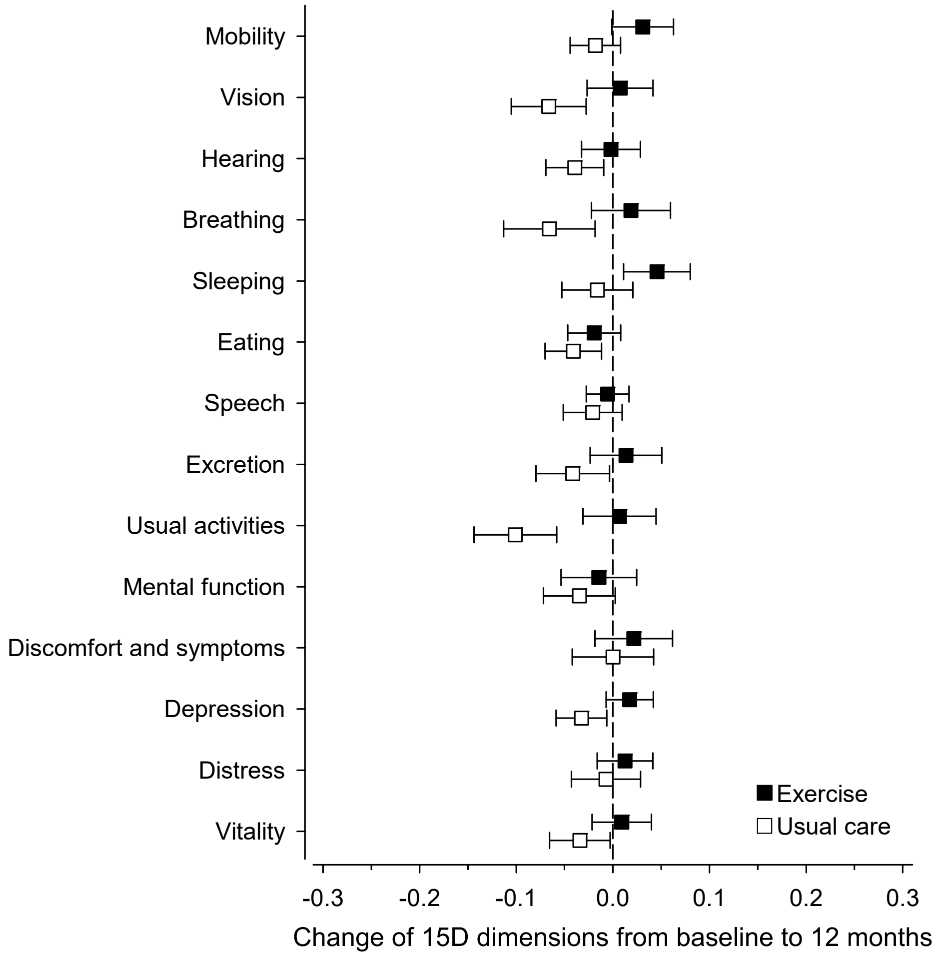

FIGURE 9 Mean change in single 15D (quality of life) dimensions from baseline to 12 months in exercise and usual care groups. Whiskers denote 95% confidence intervals. (Unpublished)

5.5 Functioning (Publication I & Publication III)

5.5.1 Functional independence and activities of daily living

At baseline, the number of frailty criteria met was inversely associated with the FIM scores. The association was seen in total FIM and its motor and cognition subsections when all the participants (n=299) were categorized into four classes according to their baseline number of frailty criteria met (Table 7). Participants who met multiple criteria had lower FIM scores than those who only met one criterion (p<0.001).

TABLE 7 Functioning (FIM) and quality of life (15D) according to frailty severity, mean (SD).

	1 criterion, n=91	**2 criteria, n=91**	**3 criteria, n=82**	**4–5 criteria, n=35**	**p-value**
FIM total	114 (8)	111 (9)	106 (10)	96 (11)	<0.001
FIM motor	82 (5)	79 (6)	76 (7)	68 (9)	<0.001
FIM cognition	32 (4)	32 (4)	30 (4)	28 (4)	<0.001
15D	0.752 (0.076)	0.710 (0.083)	0.699 (0.090)	0.640 (0.094)	<0.001

At baseline, FIM was 109 (SD 11) in both (exercise and usual care) groups. FIM deteriorated significantly from baseline to 12 months in both groups. In the exercise group, deterioration was 4.1 (95% CI: –5.6 to –2.5) points and in the usual care group 6.9 (95% CI: –8.4 to –2.3) points (Table 8). At 12 months, the exercise group performed significantly better in the individual FIM items of transferring to the bath/shower (p=0.037) and walking stairs (p=0.036) than the usual care group. The usual care group deteriorated significantly in all FIM items other than bowel management over 12 months.

TABLE 8 Changes in functional independence (FIM) and instrumental activities of daily living (IADL) from baseline to 3, 6 and 12 months in exercise and usual care groups.

Measurement	**Exercise**	**Usual care**	**p-value**
FIM			
Baseline, mean (SD)	109 (10)	109 (11)	..
Change from 0 to			
3 months, mean (95% CI)	−0.6 (−2.1 to 0.9)	−2.4 (−3.9 to −0.9)	0.10
6 months, mean (95% CI)	−2.7 (−4.2 to −1.2)	−5.7 (−7.2 to −4.1)	0.007
12 months, mean (95% CI)	−4.1 (−5.6 to −2.5)	−6.9 (−8.4 to −2.3)	0.012
IADL			
Baseline, mean (SD)	22.8 (5.5)	22.9 (6.1)	..
Change from 0 to			
3 months, mean (95% CI)	−0.4 (−0.9 to 0.1)	−1.0 (−1.5 to −0.5)	0.10
6 months, mean (95% CI)	−0.7 (−1.2 to −0.3)	−1.3 (−1.7 to −0.8)	0.16
12 months, mean (95% CI)	−1.4 (−1.9 to −0.9)	−2.1 (−2.6 to −1.6)	0.080

Analysis of the change in FIM in the pre-frail and frail subgroups revealed that all the subgroups deteriorated over 12 months (Figure 10). In the exercise group, the pre-frail subgroup deteriorated by 2.7 (95% CI –4.5 to –0.9) points and the frail subgroup by –5.9 (95% CI: –8.6 to –3.3) points. In the usual care group, the mean changes were –6.8 (95% CI: –8.7 to –4.9) for the pre-frail and –7.0 (95% CI: –9.7 to –4.2) for the frail subgroups. The change in FIM over 12 months was significantly different in the exercise and usual care groups' pre-frail subgroup (p=0.003) but there was no significant difference in the frail subgroups (p=0.60). The change in FIM over 12 months in the pre-frail and frail subgroups was significantly different in the physical exercise group (p=0.045) but not in the usual care group(p=0.91).

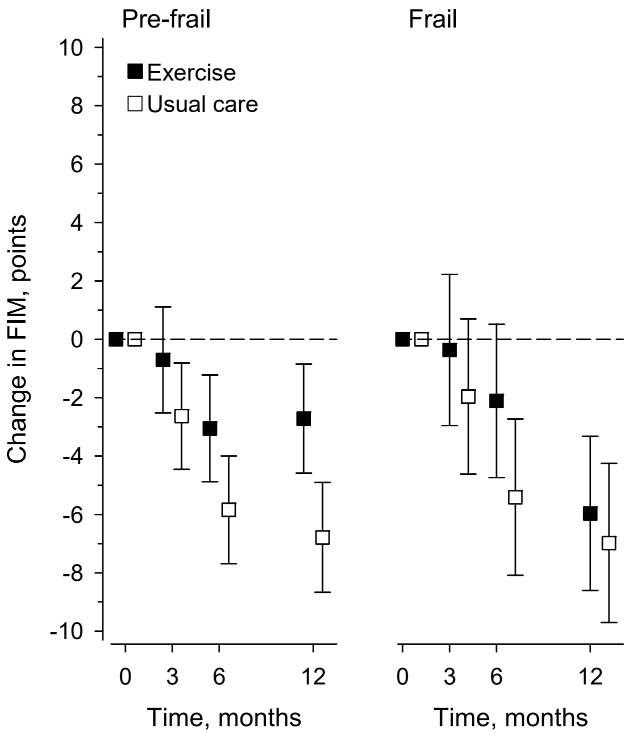

FIGURE 10 Mean change in Functional Independence Measure (FIM) scores from baseline to 3, 6 and 12 months in exercise and usual care groups and in their pre-frail and frail subgroups. (Unpublished)

There was no difference between the baseline IADL scores of the exercise group 22.8 (SD 5.5) and those of the usual care group 22.9 (SD 6.1). Over 12 months, the IADL scores deteriorated significantly in both groups, by –1.4 (95% CI: –1.9 to –0.9) points in the exercise and –2.1 (95% CI: –2.6 to –1.7) points in usual care group, and the groups did not differ from each other at 12 months (interaction, p=0.92) (Figure 11).

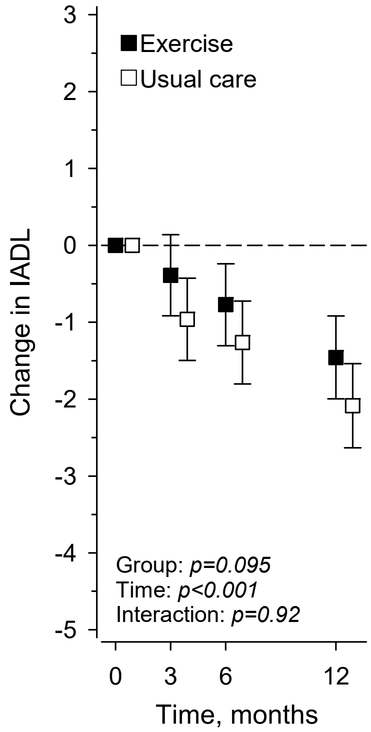

FIGURE 11 Mean change in Instrumental Activities of Daily Living (IADL) scores from baseline to 3, 6 and 12 months in exercise and usual care groups.

5.5.2 Physical performance

Physical performance was measured using the SPPB, and the baseline scores were 6.1 (SD 2.7) in the exercise group and 6.3 (SD 2.5) in the usual care group. At 12 months, the score had changed by 1.6 (95% CI: 1.3 to 2.0) points in the exercise group, and remained at baseline level (0.0, 95% CI: –0.3 to 0.3) in the usual care group (Table 9). Of the individual SPPB components, the balance and chair-rise tests differed significantly in the exercise and usual care groups over 12 months (Figure 12).

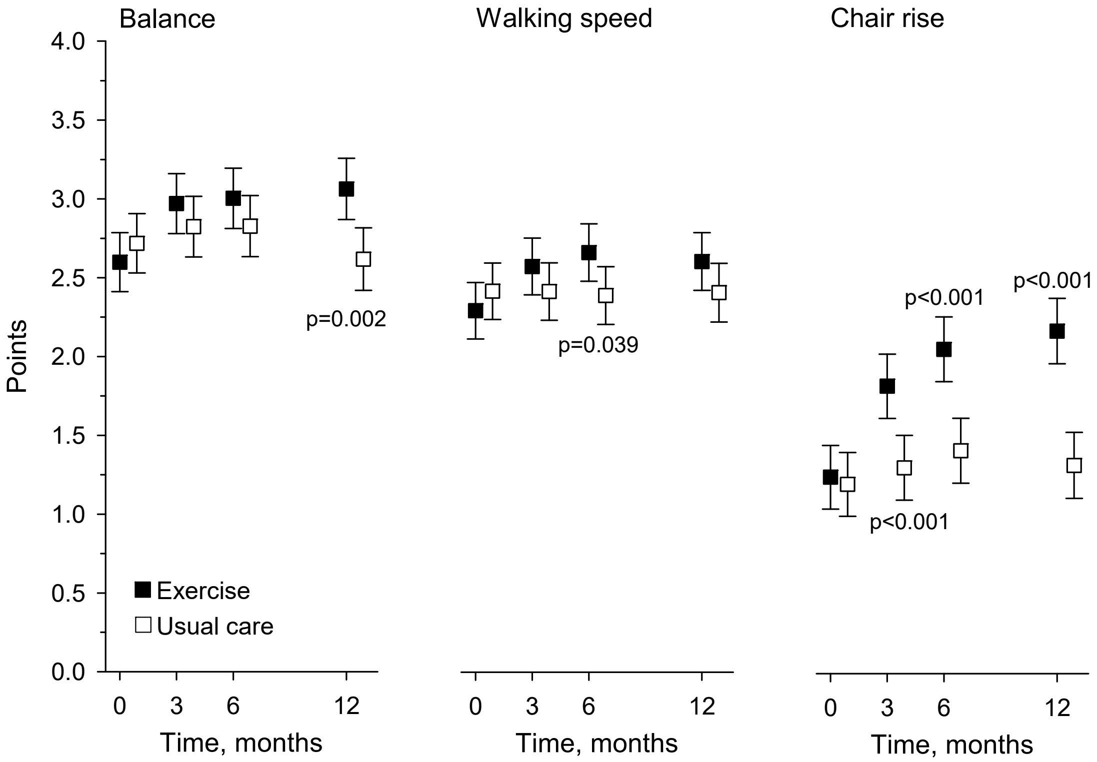

FIGURE 12 Three components (balance, walking speed, and chair-rise test) of the Short Physical Performance Battery (SPPB) and their mean scores at baseline, 3, 6 and 12 months. Whiskers denote 95% confidence intervals. (Unpublished)

Analysis of the changes in SPPB points over 12 months in the pre-frail and frail subgroups (Figure 13) revealed that in the exercise group, the pre-frail subgroup gained 1.7 (95% CI: 1.3 to 2.1) points and the frail subgroup 1.4 (95% CI: 0.9 to 1.9) points. In the usual care group, the change over 12 months was 0.03 (95% CI: –0.4 to 0.4) in the pre-frail and –0.03 (95% CI: –0.6 to 0.5) in the frail subgroup. In both subgroups, the difference between the exercise and usual care groups were statistically significant (p<0.001). The change did not differ in the pre-frail and frail participants of the exercise (p=0.39) or the usual care group (p=0.86).

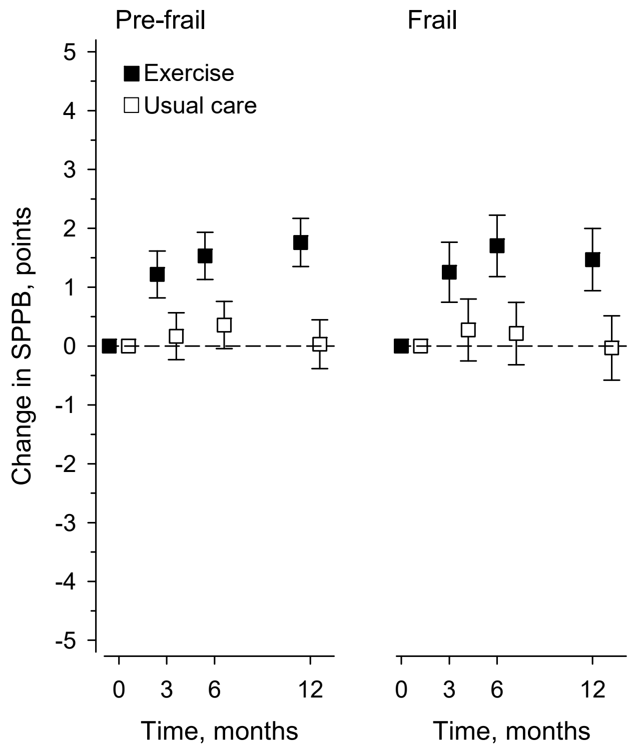

FIGURE 13 Mean change in Short Physical Performance Battery (SPPB) scores from baseline to 3, 6 and 12 months in pre-frail and frail subgroups of exercise and usual care groups. Whiskers denote 95% confidence intervals. (Unpublished)

At baseline, handgrip strength had a mean score of 18.9 kg (SD 7.8) in the exercise group and 19.7 kg (SD 7.8) in the usual care group. The change in grip strength over 12 months was not significant in the exercise (–0.5 kg, CI 95%: –1.0 to 0.1) or the usual care group (–1.2 kg, CI 95%: –1.7 to –0.6) (Table 9).

TABLE 9 Changes in physical performance in Short Physical Performance Battery (SPPB) and grip strength, kg from baseline to 3, 6 and 12 months in exercise and usual care groups.

Measurement	Exercise	Usual care	p-value
SPPB			
Baseline, mean (SD)	6.1 (2.7)	6.3 (2.5)	..
Change from 0 to			
3 months, mean (95% CI)	1.2 (0.9 to 1.5)	0.2 (–0.1 to 0.5)	<0.001
6 months, mean (95% CI)	1.6 (1.3 to 1.9)	0.3 (0.0 to 0.6)	<0.001
12 months, mean (95% CI)	1.6 (1.3 to 2.0)	0.0 (–0.3 to 0.3)	<0.001
Grip strength, kg			
Baseline, mean (SD)	18.9 (7.8)	19.7 (7.8)	..
Change from 0 to			
3 months, mean (95% CI)	0.1 (–0.4 to 0.7)	0.1 (–0.5 to 0.6)	0.89
6 months, mean (95% CI)	0.1 (–0.5 to 0.6)	–0.2 (–0.8 to 0.3)	0.43
12 months, mean (95% CI)	–0.5 (–1.0 to 0.1)	–1.2 (–1.7 to –0.6)	0.097

5.5.3 Leisure-time physical activity

At baseline, the mean number of weekly leisure-time physical activity sessions (lasting ≥30 minutes) in the exercise (2.2, 95% CI: 1.8 to 2.7) and usual care (2.2, 95% CI: 1.8 to 2.6) groups did not significantly differ. At six months, both groups reported the highest number of physical activity sessions: 3.3 (95% CI: 2.7 to 4.0) in physical exercise and 2.7 (95% CI: 2.2 to 3.2) in usual care group. The number of weekly sessions declined close to baseline level in both groups at 12 months; the exercise group reported 2.5 (95% CI: 1.9 to 3.0) and usual care 2.1 (95% CI: 1.7 to 2.5) activity sessions per week (group p=0.26; time p<0.001; interaction p=0.32).

5.5.4 Falls

Over 12 months, the participants in the physical exercise group experienced on average 1.4 (95% CI 1.2 to 1.6) falls per person-year, and participants in the usual care group 3.1 (95% CI: 2.8 to 3.4) falls per person-year (IRR 0.47, 95% CI: 0.4 to 0.55).

5.6 Frailty severity (Publication IV)

At baseline, in the exercise group, 92 (62%) participants were classified as pre-frail (1–2 criteria), 58 (38%) as frail (3–5 criteria), and the mean number of criteria met was 2.2 (SD 1.1). In the usual care group, 92 (62%) participants were pre-frail, 57 (38%) were frail, and the mean number of criteria met was 2.2 (SD 1.0).

At 12 months, the number of frailty criteria met had decreased by 0.27 (95% CI: –0.47 to –0.08) in the exercise group, whereas in the usual group it remained unchanged (0.01, 95% CI: –0.16 to 0.18). The difference between the mean change in the groups was significant (p=0.042).

Over 12 months, the prevalence of the exhaustion (p=0.009) and low physical activity (p<0.001) criteria were significantly different in the groups and the prevalence was lower in the exercise group. The prevalence of weight loss, slowness, or weakness did not change nor did it differ in the exercise and usual care groups at 12 months.

In the exercise group, of those who were pre-frail at baseline, 15 participants became non-frail, 7 frail, and 5 died. In the usual care pre-frail subgroup, 8 participants became non-frail, 20 frail, and 7 died. Of the participants who were frail at baseline in the exercise group, 35 became pre-frail, 3 non-frail, and none died. In the usual care´s frail subgroup, 17 became pre-frail, 1 non-frail, and 3 died. Transitions between frailty states (non-frail, pre-frail, frail, deceased) occurred in both groups, but there was a significant difference between the exercise and usual care group's shifts from baseline pre-frailty (p=0.032) and frailty (p=0.009).

6 DISCUSSION

Among older people with signs of frailty, a 12-month physiotherapist-supervised home-based physical exercise intervention did not increase the number of days lived at home over 24 months in comparison to those in usual care. Among those who were frail at baseline, the intervention was cost-neutral over 24 months (12-month intervention + 12-month follow-up). Over 12 months, the exercise intervention was more effective based on QALYs but more expensive than usual care. The 12-month exercise program improved physical performance, maintained quality of life, and reduced the deterioration of functional independence. Compared to usual care, the exercise intervention slowed down or reversed the progression of frailty and decreased the prevalence of two frailty phenotype criteria: exhaustion and low physical activity.

6.1 Days lived at home

The exercise interventions did not increase the number of days lived at home over the 24 months in comparison to usual care. The exercise group lived on average 21 days more at home than usual care and the difference was mainly due to days after death. More people died during the first 12 months in the usual care group, but there was no difference between the groups' mortality over 24 months. There was also no difference between the groups in placements in 24-hour care facilities. A previous study conducted in Australia (Cameron et al., 2013) of people who met 3–5 frailty phenotype criteria, had similar results. There was no difference between nursing home placements among those who participated in the 12-month intervention including home-based exercises and usual care (Cameron et al., 2013). The follow-up time of 24 months in the HIPFRA study might have been too short to detect significant differences between the groups in days lived at home. In a Finnish cohort, which was followed from the age of 70 for 22 years, people were assigned to a 24-care facility on average at the age of 85 (Salminen et al., 2017). Our participants' mean age was 82 at baseline, and they were only followed for two years. Most of our participants (61%) were pre-frail and only a minority (2%) met all the five phenotype frailty criteria at baseline. Previous studies have shown that more severe frailty is associated with nursing home placements and long-term care (Kojima, 2018). In addition, age, poor self-rated health, impaired functional (ADL and IADL) and cognitive status, previous short-term nursing home periods, and polypharmacy are strong predictors of nursing home placements (Luppa et al., 2010).

In South Karelia, the policies concerning older adults' placements into 24-hour care changed during the study period. More resources were targeted to providing services at home for older adults whose ability to continue living at home was at risk. For example, the district increased the number of physiotherapists and occupational therapists working in home rehabilitation and decreased the number of places in 24-hour care facilities and long-term wards. In 2018, the province of South Karelia had the lowest percentage of older adults living in 24-hour care facilities in Finland (Mielikäinen & Kuronen, 2019). The change in the local policies of Eksote might have had an impact on the low number of participants who were assigned to 24-hour care facilities during the study period, but it affected both randomized groups similarly.

6.2 Utilization and costs of social and health care services

We evaluated the impact of the HIPFRA exercise interventions on the costs of social and health care service utilization among older adults with signs of frailty from the care providers' perspective. Applying a 12-month physiotherapist supervised exercise program at participants' homes was not cheap, as total mean costs were EUR 7526 per participant. These intervention costs significantly increased the total expenses of the social and health care services over 12 months in the exercise group in comparison to those in the usual care group. For older adults, participation in the HIPFRA study was voluntary and free. The costs of the intervention were split between Eksote and Kela.

In the exercise group, fewer people advanced from the pre-frailty to the frailty state, and more participants improved from frailty to the pre-frailty or non-frailty state than in the usual care group. This may explain the lower utilization of social and health care services over 24 months in the exercise frail subgroup in comparison to the usual care frail subgroup, as more severe frailty is associated with higher health care utilization and costs (Bock et al., 2016; Ensrud et al., 2018; García-Nogueras et al., 2017; Hajek et al., 2018; Ilinca & Calciolari, 2015). From the health care providers' perspective, the exercise intervention was cost-neutral for the participants who were frail at baseline, as the participants in the exercise group spent fewer days in long-term primary care wards than those in the usual care frail subgroup over the 24 months. From the cost point of view, the exercise intervention increased the pre-frail subgroup's costs significantly more than those of the usual care pre-fail subgroup. Previous studies have shown that people with frailty have higher health care expenses than people who are pre-frail or robust (Bock et al., 2016; Ensrud et al., 2018; Ilinca & Calciolari, 2015). This was also seen in the HIPFRA study, as the pre-frail participant costs per person-year were lower than those of the frail participants in both randomization groups.

Hajek et al. (2018) found that the onset of exhaustion criterion was associated with higher social and health care service costs, and the other criteria had varying and inconclusive effects on different health care sectors. In the HIPFRA study, the prevalence of the exhaustion criteria was significantly lower at 12 months than at baseline in both groups, but the decrease was much larger in the exercise group. The progression of frailty severity is not linear, and the status might naturally fluctuate between worse and better over time (Gill et al., 2006; Kojima et al., 2019; Ofori-Asenso et al., 2020). Different kinds of exercise interventions have reduced the severity of frailty (Cameron et al., 2013; Tarazona-Santabalbina et al., 2016; Travers et al., 2019; Trombetti et al., 2018), and among sedentary older adults, this exercise intervention prevented the number of signs of frailty from increasing (Cesari et al., 2015) in comparison to usual care.

Even though the total costs of the social and health care services over 12 months were higher in the exercise group, the incremental cost-effectiveness analysis showed positive results. All the participants were situated in the northeast quadrant of the ICER plane, which means that exercise was more effective in terms of QALY, as the exercise group gained 0.040 QALYs more than the usual care group although their total costs were higher. In the LIFE study, sedentary older adults who were prescribed 150 minutes of physical activity per week gained 0.047 more QALYs over 2.6 years than those who received health education (Groessl et al., 2016). With a 12-month multifactorial intervention targeted at different frailty criteria among frail older adults, the Australian study found that the intervention provided better value for the money than usual care, even though it did not significantly affect QOL (Fairhall et al., 2015).

6.3 Quality of life

QOL was inversely associated with the participants' frailty status at baseline, which is in line with the findings of other studies (Henchoz et al., 2017; Kojima et al., 2016). Our exercise group maintained their baseline level QOL during the intervention year, whereas the usual care group's QOL deteriorated significantly. The deterioration in the usual care group's 15D index score was 0.037, which can be considered clinically meaningful, as a change of 0.035 in the 15D is considered substantial (Alanne et al., 2015). According to a systematic review, resistance training is a supportive factor for better QOL among older adults (Hart & Buck, 2019).

The 15D dimensions include various aspects that influence a person's QOL, such as physical (mobility, usual activities), cognitive (memory, speaking) and sensory functioning (seeing and hearing); mental health (depression, anxiety, vitality); and pain and discomfort. Over the 12 months, the vision, breathing, usual activities, depression, and vitality dimensions differed in the exercise and usual care groups, in favor of the exercise group. Exhaustion, depression, and fatigue are closely linked to vitality, as well as to each other. Previous studies have shown that exercise interventions have a positive effect on reducing depressive symptoms among different age groups (Schuch et al., 2016) and among older adults (Bigarella et al., 2021). The prevalence of the exhaustion criterion decreased in both groups over the 12 months of our study, but to a significantly greater extent in the exercise group. This was also shown in the 15D, as the groups differed in terms of depression and vitality dimensions. The frailty status was also positively impacted by the exercise interventions of the study. Previous studies have shown that more severe frailty affects QOL negatively (Kojima et al., 2016). More severely frail people have weaker functional status, poorer health (Henchoz et al., 2017), and smaller networks (Hoogendijk et al., 2015). Moreover, loneliness and isolation increase the risk of developing more severe frailty (Gale et al., 2018; Sha et al., 2020). Depression is also a risk factor for more severe frailty, and vice versa, more severe frailty is a risk factor for developing depression (Soysal et al., 2017).

6.4 Functioning

The physical exercise intervention in the HIPFRA study did not prevent a decline in basic ADL and IADL among older adults with signs of frailty. The decline in FIM was slower in the physical exercise group, and there were significant differences between the groups at six and 12 months. Not many RCTs have studied changes in FIM outside hospital settings among older adults. Two other Finnish RCTs, FINALEX (Pitkälä et al., 2013) and AGE (Hinkka et al., 2007) found a similar decrease pattern in FIM scores to that among the participants of this study. FINALEX studied 12-month supervised home- and center-based physical exercise interventions among Alzheimer patients (Pitkälä et al., 2013). AGE studied group rehabilitation in rehabilitation centers and consultations of a multidisciplinary geriatric rehabilitation team for older adults who were at a high risk of institutionalization (Hinkka et al., 2007). In addition, a 16-week physiotherapist-supervised exercise program for people with mild or moderate Alzheimer disease reduced falls, and improved lower limb strength functioning, whereas the usual care control group's performance in ADL functions decreased (Cezar et al., 2021).

The physiotherapist-supervised exercise program in the HIPFRA study improved physical performance assessed by SPPB**.** The SPPB scores in the exercise group increased both statistically and clinically significantly whereas in the usual care group the score remained unchanged. The change in the exercise group (1.6) was clinically meaningful, as the estimation of importance varied between 0.4 and 1.5 (Kwon et al., 2009) and 0.5 and 1.3 (Perera et al., 2006) points. There was no difference in the SPPB improvements between the subgroups of pre-frail and frailty, both exercise subgroups improved the SPPB scores clinically meaningful way and the usual care groups stayed in the baseline level.

The participants in the exercise group also had less falls per person-year than those in the usual care group. Our home-based intervention was based on the Otago exercise program's strength training exercises (Gardner et al., 2001), which have proven to be effective in reducing falls among older adults (Thomas et al., 2010). The number of falls is associated with SPPB scores (Lauretani et al., 2019).

All the exercise sessions were supervised by a physiotherapist, and main focus was the participant's physical performance. The main focus was on lower limbs strength training, with additional functional exercises to prolong the transfer effect of possible strength gains to everyday life. Even though the exercise sessions included functional exercises, which were targeted at important daily living tasks, none of the single FIM motor or cognition items increased over the 12 months. The groups differed at 12 months in the two FIM items of transferring to the bath/shower and walking stairs, which deteriorated significantly more in the usual care group. Both tasks require strength of the lower extremities and good balance, which both increased in the exercise group according to the SPPB measurements. The maintenance and improvements of functional independence in ADL and IADL tasks might require an occupational therapist to be part of the home-based exercise intervention. Among older adults whose home- and community-based interventions have included an occupational therapist, the interventions have succeeded in improving ADL functions (De Coninck et al., 2017). The difference between the exercise group and the usual care group's usual activities and breathing dimension in the 15D, and the slower deterioration of functional independence in the exercise group is also reflected in the improved physical performance of the exercise group. The breathing dimension of the 15D concerns shortness of breath, and it seems that the participants' better physical performance after the 12-month exercise intervention decreased their feelings of shortness of breath during daily activities.

The exercise group did not differ from the usual care group in handgrip strength results over 12 months. Neither did their prevalence of the weakness criterion change from baseline to 12 months. The exercise intervention was mainly focused on lower limbs, which may explain the no-change in the grip strength over 12 months. An earlier study of 24-week resistance exercise training among frail older adults showed that handgrip strength did not change, but leg extension strength and SPPB improved significantly (Tieland et al., 2015), which is in line with our results.

The exercise interventions did not impact on walking speed significantly or the number of participants who met the slowness criteria of the frailty phenotype. In contrast to our findings, one study found a significant difference between the usual care and exercise groups' walking speeds after a 12-month exercise program among older adults with frailty (Cameron et al., 2013). In the frailty phenotype criteria used in the HIPFRA study, the criterion for slowness was determined by the SPPB test's cut-off for one point. This meant that for a person to meet the criteria they had to take more than 8.7s to walk four meters, which equals a speed of 0.46 m/s. In the original criterion, the cutoff speeds are between 0.64 and 0.76 m/s (Fried et al., 2001). The decision to use a slower pace as a cutoff in the HIPFRA study resulted in fewer participants meeting the slowness criteria than if we had used the original cutoff. One could argue that our walking speed cutoff was too slow. The pace that a pedestrian needs to cross a zebra crossing safely, for example, is 1.2 m/s (Asher et al., 2012) and even Fried et al.´s cutoff speed has been criticized as too slow for this (Drey et al., 2011).

The physical exercise program designed by the research group included hour-long sessions twice a week with a physiotherapist for a year. Participating in exercise training for such a long time requires commitment of participants. Still, attendance of the exercise intervention was good, and participants took part in 87% of the prescribed visits. Most of the people with signs of frailty in the HIPFRA study were not physically active at baseline, as 61% reported physical activity sessions less often than once a week. The exercise intervention provided regular physical activity sessions for the exercise group, and this affected the frailty criterion of low physical activity. Although the physiotherapists also gave counseling and encouraged participants to be physically active outside the supervised exercise sessions, the number of non-supervised physical activity sessions did not differ from those in the usual care group. There was a slight increase in physical activity at six months in both groups. This may be explained by the fact that over half of the six-month assessments were conducted between June and November, and the participants might have been able to do more outside activities and walk outside between April and November when there is no snow or ice on the ground. The physiotherapist gave some counseling for the participants at their last visit how the participants could keep exercising on their own, but the physical activity levels after 12 months were not assessed.

In the relation to the ICF framework, the 12-month intervention had a positive effect on the functioning of people with signs of frailty in the body functions and structures components, as the exercise group performed better in the SPPB than the usual care group. The intervention slowed down the deterioration of functional independence, which is included in the activity component of the ICF. Of the environmental factors, the utilization of social and health care services was less in the frail subgroup of the exercise group than among the frail people in the usual care group. The intervention had no effect on days lived at home. Personal factors such as socioeconomic status were not affected by the exercise interventions.

6.5 Methodological considerations

The data used in this thesis were from HIPFRA, a larger RCT, which was conducted in South Karelia (Finland). Recruitment was conducted through advertisements in local newspapers, and home-care personnel also recruited possible participants from among their customers. This seemed to be a successful strategy, as most of the pre-frail participants were recruited through the advertisements and most of the frail participants came through the homecare personnel. The recruitment process was successful, and the targeted number of participants of 300 (based on power calculations) was achieved at the end of August 2016, four months before the recruitment deadline.

The strengths of this study were that it was rigorously performed and that it was a long-term RCT with a relatively large number of participants (n=300). The frailty status of the participants was evaluated in two phases by a health care professional using the FRAIL questionnaire (Abellan van Kan et al., 2008; Morley et al., 2012) and the frailty phenotype criteria (Fried et al., 2001), both of which are validated and used widely in frailty research (Dent et al., 2016). All the other measurements and assessments had also been previously developed and validated in previous research for use with older adults. The intervention was carried out in the real world, and in the participants' homes rather than in gyms, rehabilitation centers or research laboratories.

Participation in the exercise intervention was good. Even though the physiotherapist visits to every exercise group participant's home increased the costs of the intervention, it allowed the older adults who lived in rural area in South Karelia to also participate in the exercise program without any extra costs. Neither the participants in the exercise group nor those in the usual care group had to travel to a city or town center for the HIPFRA study assessments or the supervised exercise program. Older people might be unable to travel to center-based exercise sessions as public transportation might not be available or their health status may make it difficult for them to use it. In the light of the results, it is possible to engage sedentary people with signs of frailty in a supervised long-term physical exercise program when it is delivered at their homes.

During the year, the exercise intervention proved to be safe for older adults with frailty. There were no major adverse effects, even though the majority of the exercise participants reported some mild and transient muscle soreness and joint pain during or after exercise sessions. Any suspensions of the exercise intervention were due to acute illnesses, and most were only temporary. Even though the usual care group was able to receive rehabilitation from the local health care provider, the amount of rehabilitation received via usual care was very low. We were able to retrieve detailed information on the utilization of social and health care services from Eksote's registers, which enabled us to comprehensively calculate the cost-effectiveness of the intervention.

The primary aim of increasing home-dwelling time by six months was quite ambitious in a timeframe of 24 months. A longer follow-up and including only participants who are already frail might have been more beneficial for detecting differences in the primary outcome, as the results regarding physical performance were similar in the pre-frail and frail subgroups. If at the time of the power calculations, the data on our selected primary outcome, days at home, had been available on people with signs of frailty, the sample size calculations might have been different. The sample was large enough to detect differences between several secondary outcomes in the groups.

As limitations, the assessors were not blinded for allocation, which might have lowered the validity of the results of the outcomes elicited in the interviews. We also used frailty phenotype criteria with a few modifications to the low physical activity and slowness criteria. This is not uncommon; many studies use modified criteria (Theou et al., 2015), but it might have influenced the comparability of the studies. The functioning, QOL, and frailty measurements were performed during the intervention year (as planned), but a longer follow-up with these measurements might have been useful. The number of falls during the year were assessed by self-report, which is considered less reliable than diaries (Hannan et al., 2010) for detecting falls and can cause recollection bias.

6.6 Practical implications and future directions

The Finnish government's 2030 objectives for older adults are: improved functional capacity, higher the number of active life years, and a shorter average time needed for intensive care and nursing (The Ministry of Social Affairs and Health, Finland, 2020). The results of this thesis indicate that a 12-month supervised home-based physical exercise program for older adults with signs of frailty can make it possible to achieve these objectives. The benefits compared to usual care were seen in functioning and in QOL among both pre-frail and frail people, but the exercise did not increase days spent at home. The implementation of a 12-month physiotherapist-supervised physical exercise program twice a week is a large investment for public social and health care services. However, the investment was compensated over the following year by the decreased need for other social and health care services among the individuals who were already frail.

When people with frailty are identified, it is easier to target a cost-effective, beneficial exercise intervention toward them. To identify frailty, it is important to screen older adults in social and health care services. For the HIPFRA study, the FRAIL questionnaire and the frailty phenotype criteria were translated into Finnish, and the translated versions of these can be found in the appendix of Soukkio et al. (2020). Both FRAIL and frailty phenotype are quite easy and quick methods for identifying frail older adults.

For those who were pre-frail, exercise had a positive influence on functioning and QOL, but it was not cost neutral. It is important to find more cost-effective ways to deliver such an exercise intervention to these older adults, as they could clearly benefit from it. Performing the exercise intervention with a combination of supervised and unsupervised sessions or utilizing remote technologies might offer solutions for lowering the costs of the intervention. More research is needed to investigate the effects and cost-effectiveness of these kinds of interventions.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings can be summarized as follows:

1. The 12-month physiotherapist-supervised home-based exercise program did not increase the number of days lived at home over the 24 months in comparison to usual care among older adults with signs of frailty. Over 12 months, the exercise intervention increased the total costs per person-year of social and health care services in comparison to usual care. However, over 24 months, the exercise intervention was cost neutral, especially in the frail subgroup.
2. After 12 months, physical performance both statistically and clinically improved among the pre-frail and frail participants in the exercise group, whereas there was no change in the usual care group. The exercise did not prevent the deterioration of the functional independence or the ability to perform IADLs, but it did slow down the deterioration in the exercise group. The exercise group maintained their quality of life and the development of more severe frailty slowed down or was prevented.
3. Cost-effectiveness analyses clearly showed that the participants in the exercise group gained quality adjusted life years, but the intervention was more expensive than usual care.
4. Older adults meeting multiple frailty phenotype criteria had lower functional independence and quality of life than those who met only one or two criteria.

In conclusion, a 12-month physiotherapist-supervised, home-based exercise program should be directed at home-dwelling older adults who are already frail. The exercise intervention is cost neutral among them, and it can maintain their quality of life and increase their physical performance in comparison to usual care. Whether the long-term supervised exercise intervention should also be provided to people with pre-frailty is optional. Although it was clearly beneficial as a preventive treatment against the decline of functioning and had positive effects on quality of life and frailty severity, it was not cost neutral.

YHTEENVETO (FINNISH SUMMARY)

Ikääntyneillä henkilöillä, joilla on gerastenia, ikääntymisen mukanaan tuomat muutokset lihasvoimassa, ja muissa kehon toiminnoissa tapahtuvat nopeammin ja suuremmin kuin tavallisesti. Gerasteenisilla henkilöllä toimintakyky ja elämänlaatu on terveisiin ikätovereihinsa nähden alentunut, sekä heillä on suurempi riski joutua ympärivuorokautiseen palveluasumiseen tai kuolla. Gerastenia hidastaa myös sairauksista toipumista, lisää sairaalahoidon ja hoivan tarvetta. Lisääntynyt palveluntarve näkyy myös suurempina sosiaali- ja terveydenhuollon kustannuksina. Aikaisempien tutkimusten mukaan liikuntaharjoittelulla voidaan parantaa gerasteenisten henkilöiden fyysistä toimintakykyä, hidastaa gerastenian etenemistä sekä pienentää pitkäaikaishoidon riskiä. Tutkimustietoa pitkäkestoisen kotona toteutetun ja ohjatun liikuntaharjoittelun vaikutuksista on kuitenkin vähän ja näyttöä kotiin vietävästä ohjatusta liikuntaharjoittelusta tarvitaan lisää.

Tämä väitöstutkimus on osa suurempaa ”Kauan kotona ikääntynyt” (KauKoIKÄ, eng. HIP fracture and FRAilty, HIPFRA) -tutkimushanketta, joka on toteutettu Etelä-Karjalan sosiaali- ja terveyspiiri Eksotessa. Tutkimuksen tavoitteena oli selvittää, millaisia vaikutuksia vuoden kestävällä kotona, fysioterapeutin ohjauksessa toteutetulla liikuntaharjoittelulla on gerasteenisten henkilöiden kotona-asumisaikaan, sosiaali- ja terveyspalveluiden käyttöön ja niistä koituviin kustannuksiin, elämänlaatuun, toimintakykyyn, kaatumisiin ja gerastenian vaikeusasteeseen. Gerastenian vaikeusasteen määrittelyyn käytettiin gerastenian fenotyyppikriteeristöä, joka sisältää viisi kriteeriä, jotka käsittelevät tahatonta laihtumista, heikkoutta, hitautta, vähäistä fyysistä aktiivisuutta sekä uupumusta. Jos henkilö täyttää kriteereistä 3–5 hänellä on gerastenia, jos hän täyttää 1–2 kriteeriä hänellä katsotaan olevan gerastenian esiaste.

Tutkittavia, joilla oli gerastenia tai gerastenian esiaste, rekrytoitiin yhteensä 300 joulukuun 2014 ja elokuun 2016 välisenä aikana Etelä-Karjalan alueelta. Tutkittavat satunnaistettiin kahteen ryhmään: fysioterapeutin ohjaamaan vuoden kestoiseen kotiharjoitteluun (60 minuuttia kahdesti viikossa) (n=150) sekä tavanomaiseen hoitoon (n=150). Kotiharjoittelu toteutettiin fysioterapeutin ohjauksessa ja se eteni progressiivisesti. Harjoittelu sisälsi yksilöllisesti suunniteltuja voima-, tasapaino-, liikkuvuus- ja toiminnallisia harjoitteita. Lihasvoimaharjoitteiden vastuksena käytettiin nilkkapainoja, kahvakuulia, käsipainoja, painoliivejä sekä harjoitteluun soveltuvia kodin esineitä. Lisäksi tutkittaville annettiin tarvittaessa ravitsemus- ja liikuntaneuvontaa. Tutkittavalla kävi pääsääntöisesti sama fysioterapeutti koko tutkimusvuoden ajan ja harjoittelun toteutuksesta vastasivat kilpailutuksen perusteella valittujen yksityisten fysioterapiayritysten 24 fysioterapeuttia.

Päätulosmuuttujana tutkimuksessa oli kotona vietetyt vuorokaudet 24 kuukauden aikana. Toissijaisina tulosmuuttujina toimivat sosiaali- ja terveyspalveluiden käyttö sekä niiden kustannukset, fyysinen toimintakyky, elämänlaatu sekä gerastenian vaikeusaste. Kotona vietettyjä vuorokausia vähensivät vuorokaudet sairaalassa ja terveyskeskuksen vuodeosastoilla, tehostetutussa palveluasumisessa sekä kuolema. Tiedot hoitovuorokausista sekä muusta sosiaali- ja terveyspalveluiden käytöstä (sisältäen kaikki hoitokontaktit ja -jaksot perus- sekä erikoissairaanhoidossa) haettiin Eksoten potilastieto- ja asiakasrekistereistä 24 kuukauden ajalta tutkimukseen satunnaistamispäivästä alkaen. Kustannukset laskettiin palveluntuottajan näkökulmasta ja kustannukset määritettiin valtakunnallisen keskihinnan mukaan. Muiden muuttujien osalta tutkittaville tehtiin tutkimushaastattelut ja -mittaukset heidän kotonaan alussa, kolmen, kuuden ja 12 kuukauden kohdalla. Käytetyt mittarit: Elämänlaatu (15D-kysely), lyhyt fyysisen suorituskyvyn testistö (SPPB), itsenäinen toimintakyky ja avuntarve (FIM), välineelliset päivittäistoiminnot (IADL), käden puristusvoima (Saehan-dynamometri), kaatumisten lukumäärä ja liikunta-aktiivisuuden useus sekä gerastenian fenotyyppikriteerit.

Tutkimukseen soveltuvuus arvioitiin yhteensä 520 henkilöltä, ja heistä 300 täytti hyväksymiskriteerit ja heidät satunnaistettiin tutkimukseen. Satunnaistuksen jälkeen yksi tutkittava tavanomaisen hoidon ryhmästä ilmoitti, ettei halua jatkaa tutkimuksessa ja kielsi hänestä kerätyn tiedon käytön tutkimustarkoituksessa. Lopullinen tutkittavien määrä oli siten 299. Tutkittavat olivat keski-iältään tutkimuksen alussa 82,5 (KH 6,3) vuotta, 75 % heistä oli naisia, 39 %:lla oli gerastenia ja 61 %:lla oli gerastenian esiaste.

Tutkittavien 24 kk:n kotona-asumisaika ei eronnut ryhmien välillä: harjoitteluryhmä asui kotona keskimäärin 659 vrk (95 % LV: 635; 683) ja tavanomaisen hoidon ryhmä 638 vrk (95 % LV: 611; 665); ilmaantumistiheyksien suhde (IRR) 1,03 (95 % LV: 0,98; 1,09). Vuoden ohjatusta kotiharjoittelusta johtuen harjoitteluryhmän sosiaali- ja terveyspalveluiden kustannukset olivat 1,60-kertaiset (95 % LV: 1,23; 1,98) henkilövuotta kohti 12 kuukauden aikana ja 1,23-kertaiset (95 % LV: 0,95; 1,50) 24 kuukauden aikana tavanomaiseen hoitoon verrattuna. Niillä tutkittavilla, jotka täyttivät alkutilanteessa 3–5 gerastenian kriteeriä, harjoittelu oli kustannusneutraalia, kun 24 kuukauden kustannukset otettiin huomioon. Kustannukset henkilövuotta kohden olivat kotiharjoitteluryhmässä 32 507 € (SE 3625) ja tavanomainen hoidon ryhmässä 31 979 € (SE 3597). Esigerastenian alaryhmässä (1–2 gerasteniakriteeriä) harjoitteluryhmän 24 kuukauden kustannukset henkilövuotta kohden olivat 1,46-kertaiset (95 % LV: 1,03; 2.06) tavanomaiseen hoitoon verrattuna.

Inkrementaalinen kustannusvaikuttavuusanalyysi (ICER) osoitti, että 12 kuukauden kotiharjoittelu oli kalliimpaa, mutta tehokkaampaa kuin tavanomainen hoito. Harjoitteluryhmä säilytti elämänlaatunsa lähtötilanteen tasolla myös 12 kuukauden kohdalla, mutta tavanomaisen hoidon ryhmässä elämänlaatu laski kliinisesti ja tilastollisesti merkitsevästi.

Toimintakyvyn osalta kotiharjoittelu hidasti itsenäisen toimintakyvyn alenemista, paransi fyysistä suorituskykyä ja vähensi kaatumisten lukumäärään henkilövuotta kohden. Lähtötilanteessa kotiharjoitteluryhmän FIM-pisteet olivat 109 (KH 10) ja tavanomaisen hoidon ryhmässä FIM oli 109 (KH 11). 12 kuukauden kuluttua FIM-pistemäärä aleni molemmissa ryhmissä: kotiharjoitteluryhmässä keskimäärin –4,1 (95 % LV: –5,6; –2,5) pistettä ja tavanomaisen hoidon ryhmässä –6,9 (95 % LV: –8,4; –2,3). Ero ryhmien välillä 12 kuukauden kohdalla oli merkitsevä. Lähtötilanteessa kotiharjoitteluryhmän keskimääräiset IADL-pisteet olivat 23 (KH 5) ja tavanomaisen hoidon ryhmässä 23 (KH 6). IADL-pisteet alenivat molemmissa ryhmissä, harjoitteluryhmä –1,4 (95 % LV: –1,9; –0,9) pistettä, tavanomainen hoito –2,1 (95 % LV: –2,6; –1,6) pistettä, eikä ryhmien välillä ollut eroa muutoksessa; p=0,095.

Lähtötilanteessa kotiharjoitteluryhmän SPPB-pisteet olivat 6,1 (KH 2,7) ja vastaavasti tavanomaisen hoidon ryhmässä 6,3 (KH 2,5). 12 kuukauden aikana SPPB tulos parani kotiharjoitteluryhmässä keskimäärin 1,6 (95 % LV: 1,3; 2,0) pistettä, mitä voidaan pitää myös kliinisesti merkittävänä muutoksena toimintakyvyssä. Vastaavaa muutosta ei tapahtunut tavanomaisen hoidon ryhmässä (muutos 0,01 (95 % LV: –0,3; 0,3 pistettä). Lähtötilanteessa kotiharjoitteluryhmän käden keskimääräinen puristusvoima oli 18,9 kg (KH 7,8) ja tavanomaisen hoidon ryhmässä 19,7 kg (KH 7,8). Puristusvoimassa ei ollut merkitsevää eroa 12 kuukauden kuluttua (harjoitteluryhmän muutos –0,5 (95 % LV: –1,0; 0,1) kg ja tavanomaisen hoidon ryhmässä –1,2 (95 % LV: –1,7; –0,6) kg; p=0,26).

Vuoden aikana kotiharjoitteluryhmällä oli 1,4 kaatumista/henkilövuosi, mikä on merkitsevästi alhaisempi (IRR 0,47, 95 % LV: 0,40; 0,55; p<0,001), kuin tavanomaisen hoidon ryhmässä, jossa tapahtui 3,1 kaatumista/henkilövuosi. Verrattuna tavanomaisen hoidon ryhmään, liikuntaharjoitteluryhmässä useammalla tutkittavalla gerastenian eteneminen hidastui, esigerastenia ei edennyt gerasteniaan, gerastenia muuttui esi-gerasteniaksi tai tutkittava ei täyttänyt yhtään gerastenian kriteeriä enää 12 kuukauden kohdalla

Henkilöillä, joilla on jo gerastenia, fysioterapeutin ohjaama kotiharjoittelu 12 kuukauden ajan oli kustannusneutraalia, kun myös seurantavuoden sosiaali- ja terveyspalveluiden käyttö otetaan huomion. Sekä esigerasteeniset että gerasteeniset henkilöt hyötyvät ohjatusta liikuntaharjoittelusta, he voivat kotiharjoittelun avulla säilyttää elämänlaatuaan sekä parantaa fyysistä suorituskykyään. Kotona-asumisaikaa vuoden kestäneellä progressiivisesti edenneellä kotiharjoittelulla ei voitu kuitenkaan lisätä. Asumisaikaa seuratiin vain kaksi vuotta, mikä saattoi olla liian lyhyt ajanjakso erojen havaitsemiseen ryhmien välillä. Gerastenian seulonta on hyvä ottaa sosiaali- ja terveydenhuollossa osaksi ikääntyneen arviointi, jotta vaikuttava kuntoutus saadaan ohjattua ja kohdennettua oikein.

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ORIGINAL PAPERS

I

OLDER PERSONS WITH SIGNS OF FRAILTY IN A HOME-BASED PHYSICAL EXERCISE INTERVENTION: BASELINE CHARACTERISTICS OF AN RCT

by

Suikkanen, S., Soukkio, P., Pitkälä, K., Kääriä, S., Kautiainen, H., Sipilä, S., Kukkonen-Harjula, K., & Hupli, M. 2019

Aging Clinical and Experimental Research 31(10):1419-1427

https://doi.org/10.1007/s40520-019-01180-z

Older persons with signs of frailty in a home-based physical exercise intervention – baseline characteristics of an RCT

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Version 2. (revised) Finaldraft

Abstract

Background: Increasing the level of physical activity among persons with signs of frailty improves physical functioning. There is a lack of long-term supervised physical exercise intervention studies including a validated definition of frailty.

Aims: To present baseline characteristics of persons with signs of frailty participating in a randomized long-term home-based physical exercise trial (HIPFRA), and to study associations between the severity of frailty, functional independence and health-related quality-of-life (HRQoL).

Methods: Three hundred persons, ≥ 65 years old and with signs of frailty, (assessed by Fried´s phenotype criteria) were recruited from South Karelia, Finland and randomized to a 12-month physiotherapist-supervised home-based physical exercise programme (n=150), and usual care (n=150). Assessments at the participants' homes at baseline, and after three, six and 12 months included the Short Physical Performance Battery (SPPB), the Functional Independence Measure (FIM), HRQoL (15D) and the Mini-Mental State Examination (MMSE).

Results: Eligibility was screened among 520 persons; 300 met the inclusion criteria and were randomized. One person withdrew consent after randomization. A majority (75%) were women, 182 were pre-frail and 117 frail. The mean age was 82.5 (SD 6.3) y, SPPB 6.2 (2.6), FIM 108.8 (10.6) and MMSE 24.4 (3.1) points, with no significant differences between the study groups. Inverse associations between the severity of frailty vs. FIM scores and HRQoL ($p<0.001$ for both) were found.

Conclusions: Our participants showed marked physical frailty without major disabilities. The severity of frailty seems to be associated with impaired functional independence and HRQoL.

Trial registration: ClinicalTrials.gov NCT02305433

Key words: frailty, exercise, disability, health-related quality-of-life, community-dwelling older people

1 Introduction

Frailty syndrome is characterized by diminished strength, endurance and reduced physiological functions, and can lead to vulnerability, disability, falls, long-term care and mortality [1, 2]. Frailty occurs more commonly in women. Its prevalence increases with age, varying between 4-59% depending on the definition and the population studied [3]. A consensus of opinion on how to screen, define and assess frailty has not been reached [4]. Various methods can be used to screen and identify persons with signs of frailty, for example Fried´s frailty phenotype [5], the Frailty Index [6] and the FRAIL questionnaire [7]. Fried´s frailty phenotype criteria [5] are often used to assess physical frailty, and there are five items: 1) unintentional weight loss, 2) low physical activity, 3) exhaustion, 4) weak grip strength and 5) slow walking speed. If a person meets one or two criteria, he/she is considered as pre-frail, and if a person meets three or more criteria he/she is considered as frail [5].

One characteristic of frailty is a low physical activity level [5]. Increasing physical activity among frail persons improves physical functioning (e.g. strength, mobility, balance, and flexibility) [8]. Short-term multicomponent exercise programmes have improved physical functioning [9], frailty status [9], and quality-of-life [10] in frail persons. A longer duration of training (more than five months) seems to have greater effects on health than shorter ones in frail older adults [11]. Older adults feel that it is safer to exercise when training is supervised [12], and under supervision the intensity can be higher [13]. Further benefits of physical training in frail persons may result from individualized programmes, which seem to have greater effects on mobility and physical functioning than group exercises [14]. However, there is a scarcity of exercise trials that have involved the use of validated definitions of frailty. In particular, there is a lack of long-term supervised physical exercise trials. Along with our study, the ongoing SPRINTT trial [15] is targeted on physically frail and sarcopenic older people, with the aim of filling this gap

Our randomized controlled study HIPFRA is a real-life long-term supervised physical exercise study, targeted on home-dwelling, well-defined pre-frail and frail older adults and designed to assess the effects of physical exercise training on the duration of residing at home, and on functioning and health-related quality-of-life. The aim of this report is to describe baseline characteristics and associations between the severity of frailty vs. functional independence and quality-of-life in a-randomized controlled trial involving long-term supervised home-based physical exercise.

2 Methods

2.1 Design

Our frailty group is part of the HIPFRA study [16], which is a randomized controlled trial carried out to investigate the effects of 12-month supervised physical exercise intervention on the days lived at home in a 24-month period (the primary outcome). Secondary outcomes are physical functioning, health-related quality-of-life (HRQoL), severity of frailty, and use of social and health-care services. The intervention group participates in supervised home-based physical exercise (60-minute sessions twice a week) for 12 months, and the usual care group continues to live as usual. The hypothesis is that physical exercise intervention postpones institutionalisation and increases the time living at home by six months. The trial received approval from the Coordinating Ethics Committee of Helsinki University Hospital, Finland and is registered at ClinicalTrials.gov (NCT02305433). Participation was voluntary and persons interested received comprehensive oral and written information about the study-For a more detailed description see Soukkio et al. 2018 [16].

2.2 Participants and randomization

Participants were recruited from the South Karelia Social and Health Care District (population 131,000), Finland, starting in December 2014. They were informed about the study by way of flyers and advertisements in local newspapers, and by health care personnel. Inclusion criteria were age ≥65 years, home-dwelling (with or without home care services), able to walk independently inside with or without a mobility aid, ≥17 points in the Mini-Mental State Examination (MMSE) [17] and ability to communicate in Finnish. To be eligible the persons interested in participating needed to score at least one point in the FRAIL questionnaire [7], and fulfil at least one of the five frailty phenotype criteria [5] (Table 1).

Exclusion criteria were residing permanently in institutional care, and severe or advanced diseases, that prevented participation in physical exercise, such as severe neurological or cardiovascular disease with severely impaired physical capacities (NYHA class III or IV), severe or acute mental problems, alcohol or drug abuse, severe problems with hearing or eyesight or terminal illnesses.

The participants were first screened with by using the FRAIL questionnaire [7]. This questionnaire contains five items fatigue (How often during the past four weeks did you feel tired?), resistance (By yourself and not using aids do you have difficulty walking up 10 steps without resting?), ambulation (By yourself and not using aids, do you have any difficulty walking 300 meters?), physician-diagnosed illnesses (a list of 11 illnesses), and loss of weight (more than 5% from the previous year's weight). If the person scored one or more points, he/she continued to the next phase of recruitment.

The study nurse checked the person's eligibility to take part in the study, and verified frailty status and severity by using Fried´s frailty phenotype criteria (with slight modifications) [5] (Table 1). Eligible persons signed an informed consent document and the baseline assessments were performed at the participant's home. After baseline assessments, the participants were randomized to two groups: physiotherapist-supervised home-based physical exercise training (n=150), and usual care (n=150). Randomization was performed by using a computer generated random allocation sequence with varying block sizes.

2.3 Assessments

A more detailed description of the assessments can be found elsewhere [16]. The primary outcome measure, time residing at home (over a period of 24 months) was assessed from the South Karelia Social and Health

Care District's patient records and registers. In-patient care, hospital days, and institutionalised care (nursing home, sheltered housing) are considered as days not lived at home.

Secondary outcome measures are assessments performed at the participant's home at baseline, and after three, six and 12 months by the study physiotherapist or the study nurse, both trained to perform them. Each assessment visit takes about 1.5 hours; and consists of a structured interview, questionnaires and measurements.

Physical functioning was assessed by using the Short Physical Performance Battery (SPPB) [18], the Functional Independence Measure (FIM) [19], and Lawton's instrumental activities of daily living (IADL) [20], and grip strength was measured with a Saehan dynamometer (model Sh5001, South Korea). Cognition was assessed by using the MMSE [17], depressive symptoms with the Geriatric Depression Scale (GDS-15) [21], and nutritional status by using the Mini Nutritional Assessment (MNA) [22]. IADL, FIM, GDS-15 and MNA data were assessed by interviewing the participant. To assess HRQoL the participant answered the 15D questionnaire [23]. Weight (Omron HN289 equipment, Japan) and height (KaWe Person-Check equipment, Germany) were measured, and body mass index (BMI) was calculated. Regularly used medications and diseases diagnosed by a physician were asked about. Information was completed from electronic medical records, and the Charlson comorbidity index (CCI) [24] was calculated.

Demographic factors such as age, marital status, education and former occupation, form of living, and use of home and home health-care services were inquired about in the baseline interview. Perceived health, mobility ability and physical fitness were asked about using questions from the Finnish Elderly Health survey [25]. Lifestyle habits were investigated: physical activity as weekly frequency of activity sessions lasting for more than 30 minutes, and smoking habits as the daily amounts of cigarettes and other products. Perceived pain was assessed by inquiring "Are you experiencing any pain at the moment or during the day?". The number of falls was investigated by asking "Have you fallen during the previous three months and if you did, did you have any associated injuries?".

2.4 Statistical analyses

Statistical comparisons between the randomization groups were made by using t-test and the $\chi 2$ test, as appropriate. Statistical significances for the unadjusted hypothesis of linearity across categories of frailty severity of the study participants were evaluated by using analysis of variance (ANOVA) with an appropriate contrast (orthogonal polynomial). The bootstrap method was used when the theoretical distribution of the test statistics was unknown or in cases of violation of the assumptions (e.g. non-normality). The normality of the variables was tested by using the Shapiro-Wilk W-test. The Stata 15.0, StataCorp LP (College Station, TX, USA) statistical package and IBM SPSS statistics 25.0 were used for the analyses. In the analyses two frailty categories (scores 4 and 5) were combined to achieve an appropriate amount of persons. The level of statistical significance was set at 0.05 in all analyses. For statistical power calculation see Soukkio et al. (2018) [16].

3 Results

3.1 Recruitment and baseline characteristics

Five-hundred and twenty persons were screened by using the FRAIL questionnaire. Of these 43% were screened by the health care personnel and 57% by the study personnel. Of the screened persons, 224 women and 76 men met all the inclusion criteria and were willing to participate (Fig. 1). One person withdrew their informed consent after randomization and denied use of the data, decreasing the number of participants in the usual care group to 149. The mean age was 82.5 years, (range 65 to 98). According to the frailty criteria 182 participants were pre-frail (one or two criteria of the five fulfilled), and 117 were frail (3-5 criteria fulfilled) at baseline. Nine participants fulfilled all five frailty criteria (Table 1). The mean SPPB score was 6.2 (SD 2.6), and the mean FIM total score was 108.8 (10.6). Of the participants, 239 (80 %) used a rollator walker or stick. One hundred and seventy-four (58%) lived alone, and 25% received home care or home health care services organized through the hospital district. The groups were similar in their baseline characteristics (Table 2).

Fig. 1 Flowchart of the study

Table 1. Frequency of frailty criteria and their distribution in the physical exercise and usual care groups. The p-values refer to a difference between the randomization groups.

Frailty phenotype criteria [a]	**Participants meeting the criteria, n, (%)**			
	All (n= 299)	**Physical exercise** (n=150)	**Usual care** (n=149)	**p-value**
Unintentional weight loss				
more than 5 % (vs. weight 12 months ago)	53 (18)	26 (17)	27 (18)	0.86
Low physical activity [b]				
Under 30 minutes per week	160 (54)	77 (51)	83 (66)	0.45
Exhaustion				
Answering "moderate amount" or "most of the time" to one or both questions: How often did you feel that…	186 (62)	90 (60)	96 (64)	0.43
a) everything you did was an effort?	141 (47)	64 (43)	77(52)	
b) you could not get going?	122 (41)	59 (39)	63 (42)	
Weakness				
Weak grip strength under cut-off value [c]	179 (60)	94 (63)	85 (57)	0.32
Slowness				
Gait speed [d] < 0.46 m/s	81 (27)	48 (32)	33 (22)	0.051

[a] Slightly modified, [b] Minutes per week were used instead of kcal per week. Our question was "How often did you exercise during the previous three months?", [c] Cut-off values (stratified by BMI and gender): for women with BMI ≤ 26.0 kg/m^2, cut-off ≤ 17 kg; BMI 26.1-29.0 kg/m^2, cut-off ≤ 18 kg; BMI >29.0 kg/m^2, cut-off ≤ 21 kg. For men with BMI ≤ 24.0 kg/m^2, cut-off ≤ 29 kg; BMI 24.1-28.0 kg/m^2, cut-off ≤ 30 kg; BMI >28.0 kg/m^2 cut-off ≤ 32 kg ,[d] Normal gait speed, walking aid allowed, cut-offs, at 4 m >8.7 s and at 2.44 m > 5.2 s.

Table 2. Baseline characteristics of all participants and in the randomized groups (physical exercise and usual care). Frequencies (%) or means (SD) are shown. Values of p refer to differences between the randomization groups.

Characteristics	All (n=299)	Physical exercise (n=150)	Usual care (n=149)	p-value
Women, n (%)	224 (75)	114 (76)	110 (74)	0.67
Age, mean (SD)	82.5 (6.3)	82.2 (6.3)	82.7 (6.3)	0.44
BMI [a] (kg/m^2), mean (SD)	28.5 (5.9)	28.4 (5.5)	28.6 (6.1)	0.78
Marital status, n (%)				0.19
Married/in a relationship	118 (39)	56 (37)	62 (42)	
Single/divorced	46 (15)	19 (13)	27 (18)	
Widowed	135 (45)	75 (50)	60 (40)	
Education <9 years, n (%)	195 (63)	99 (66)	90 (60)	0.32
MMSE [b], mean (SD)	24.4 (3.1)	24.2 (3.1)	24.6 (3.2)	0.39
Severity of frailty [c]				0.94
Pre-frail, 1-2 of the 5 criteria, n (%)	182 (61)	91 (61)	91 (61)	
Frail, 3-5 of the 5 criteria, n (%)	117 (39)	59 (39)	58 (39)	
Physician-diagnosed diseases or disorders, n (%)				
Coronary heart disease	128 (43)	57 (38)	71 (48)	0.09
Stroke or TIA [d]	70 (23)	37 (25)	33 (22)	0.61
Hypertension	220 (74)	110 (73)	110 (74)	0.92
Musculoskeletal diseases [e]	253 (85)	129 (86)	124 (83)	0.51
Respiratory diseases (COPD [f], asthma)	36 (12)	16 (11)	20 (13)	0.46
Depressive symptoms	50 (17)	25 (17)	25 (17)	0.98
Alzheimer's disease or other dementias	41 (14)	19 (13)	22 (15)	0.60
CCI [g], mean (SD)	2.0 (1.7)	2.0 (1.7)	2.0 (1.7)	0.84
Number of regular medications, mean (SD)	6.8 (3.1)	6.7 (3.2)	7.0 (3.1)	0.43
Walking aids, n (%)	239 (80)	122 (81)	117 (79)	0.54
Walking sessions (> 30 minutes) weekly, n (%)				0.11
4-7 times	37 (12)	15 (10)	22 (15)	
1-3 times	79 (26)	47 (31)	32 (21)	
<1 time	183 (61)	88 (59)	95 (64)	
Grip strength [h] (kg), mean (SD)				
Women	16.5 (5.5)	16.3 (5.7)	16.7 (5.3)	0.53
Men	27.7 (7.6)	27.3 (7.6)	28.2 (7.7)	0.61
SPPB [i], mean (SD)	6.2 (2.6)	6.1 (2.7)	6.3 (2.5)	0.49
FIM [j], mean (SD)				
Total	108.8 (10.6)	108.8 (10.3)	108.8 (10.9)	0.97
Motor	78.0 (7.8)	78.0 (7.6)	78.0 (8.0)	0.92
Cognition	30.9 (4.0)	30.9 (4.0)	31.0 (3.9)	0.85
HRQoL 15D [k], mean (SD)	0.712 (0.091)	0.719 (0.084)	0.705 (0.097)	0.19
GDS-15 [l], mean (SD)	4.8 (2.7)	4.7 (2.5)	4.9 (2.8)	0.64
MNA [m], mean (SD)	23.1 (3.2)	23.3 (3.1)	22.7 (3.4)	0.15
Falls during the previous 3 months, n (%)				0.89
none	192 (64)	98 (65)	94 (64)	
1-2	80 (27)	40 (27)	40 (27)	
≥ 3	26 (9)	12 (8)	14 (9)	
Perceived pain [n], n (%)	217 (73)	103 (69)	114 (77)	0.07

[a] BMI, Body Mass Index; [b] MMSE, Mini-Mental State Examination [17]; [c] Severity of frailty measured with modified Fried´s phenotype criteria[5]; [d] TIA, Transient Ischaemic Attack; [e] Musculoskeletal diseases, at least one of the following: arthritis, osteoporosis, rheumatoid arthritis, low back pain; [f] COPD, Chronic Obstructive Lung Disease; [g] CCI, Charlson Comorbidity Index [24]; [h] Mean of the best values (of three tries) from both hands; [i] SPPB, Short Physical Performance Battery [18]; [j] FIM, Functional Independence Measure [19]; [k] Health-related quality-of-life questionnaire (15D) [23]; [l] GDS-15, Geriatric Depression Scale- 15 [21]; [m] MNA, Mini Nutritional Assessment [22]; [n] Answering "yes" to the question, "Are you experiencing any pain at the moment or during the day?".

3.2. Severity of frailty, and functional independence

The severity of frailty was inversely and linearly associated with FIM scores (Fig. 2). With an increase in the number of frailty criteria met, FIM scores decreased. In the pre-frail participants the mean FIM score was 113 (SD 8) and in the frail persons it was 103 (11) (p for linearity <0.001). The same pattern was seen in both FIM subcomponents; in the motor component the mean score in the pre-frail persons was 81 (SD 6) and in the frail persons 74 (9) (p for linearity < 0.001), and in the cognition component the mean scores were 32 (4) and 30 (4) (p < 0.001), respectively.

Fig. 2 FIM (Functional Independence Measure) scores (total, cognition and motor) by categories of frailty severity (frailty scores 1, 2, 3, and 4-5) at baseline. Mean (95 % CI). The total number of participants was 299, of whom 91 persons were in category 1, 91 in category 2, 82 in category 3, and 35 in category 4-5. Values of p are for linearity across frailty categories

3.3. Severity of frailty, and health-related quality-of-life

An inverse association between severity of frailty and HRQoL was also seen (Fig. 3). Those who were frail (scores 3-5) had lower scores in the 15D questionnaire, indicating worse quality-of-life compared with persons with pre-frailty (p for linearity <0.001).

Fig. 3 Health-related quality-of-life (15D) scores by categories of frailty severity (frailty scores 1, 2, 3, and 4-5) at baseline. Mean (95% CI). The total number of participants was 299, of whom 91 persons were in category 1, 91 in category 2, 82 in category 3, and 35 in category 4-5. Values of p are for linearity across frailty categories

4 Discussion

We recruited 300 persons with signs of frailty and randomized them to physical exercise and usual care groups. We were able to recruit both pre-frail and frail persons. The participants' physical functioning at baseline according to SPPB scores was impaired while most of them did not have major problems in functional independence. The severity of frailty was linearly associated with both physical functioning and HRQoL.

Slightly modified phenotype criteria were used to detect older persons with signs of frailty. During the recruitment process, we were able to recruit a high number of physically frail older adults from the area of South Karelia. Recruitment had two main sources; advertisements and health-care personnel. The personnel's information about eligible candidates was important for us to find those more severely physically frail persons. On the other hand, persons who contacted us directly were usually in better condition.

According to the frailty characteristics, our participants were markedly physically frail. A majority of participants were pre-frail (61%) with low SPPB scores, which gives us an opportunity to observe changes in frailty status during the intervention year. In our trial the two most prevalent frailty criteria were weakness

(60%) and exhaustion (62%). Findings from two large population-based studies [26] revealed that weakness was the first frailty criterion, occurring as early as nine years prior to the onset of frailty, while low physical activity and slowness occurred six years prior to onset. The last frailty criterion occurring at or before the onset of frailty was weight loss [26]. Among our participants, the occurrence of weight loss was only 18%, being in line with the results of other studies [5, 27].

The participants' mean age was high, they suffered from multiple diseases and often reported polypharmacy, most of them lived alone and a very high proportion (80%) used mobility devices. Even though the majority of our participants were pre-frail, their mean SPPB scores were relatively low compared with those reported in the LIFE [28], and SPRINTT [29] studies, and by Tarazona-Santabalbina et al.[9], reflecting our participants' prevailing physical frailty, which can be considered as a strength of this study. On the other hand, the SPRINTT [29] and LIFE [30] studies did not involve participants needing mobility devices, and frailty phenotype as an inclusion criterion was not used.

The mean FIM score of 109 among our participants indicates fairly independent functioning compared for example, with that in Finnish Alzheimer exercise trial, where the mean FIM score was 87 [31]. A declining FIM score reflects more dependence on help from others in everyday chores. In our study an inverse association between the severity of frailty and functional independence was observed. A negative association has been found between Edmonton Frailty Scale (EFS) and FIM scores in patients at discharge from a short-term geriatric ward [32]. To our knowledge the association between frailty and FIM scores has not been studied before in community-living older adults. It seems that the severity of frailty also shows an inverse association ~~also~~ with HRQoL and our findings are in line with those in previous studies [33, 34].

A strength of our study is that it is a rigorously performed randomized controlled trial, in real life. The participants are truly physically frail or pre-frail thus indicating neither ceiling nor floor effects on our outcomes. Another strength is that we used validated measurements and questionnaires. The research physiotherapist and the nurse were trained to perform the assessments and are monitored. Assessments and the intervention are performed in the participants' homes, so they need no transportation. As a weakness, the study assessors cannot be blinded since they participated in scheduling the trial although they do not administer the exercise intervention. Furthermore, our primary aim of increasing the duration of home-living by six months is relatively large. However, this frail population is at high risk of use of hospital and other institutional care. The risk of contamination of the groups is relatively low since the participants' baseline physical activity is very low and the supply of physiotherapy for this patient group is limited in public health care.

5 Conclusions

Recruitment of the participants was successful. At baseline the characteristics of the two groups were similar. The participants were physically frail or pre-frail according to modified Fried´s phenotype criteria. The occurrence of the five frailty phenotype criteria were in line with the findings of other studies. An increase in the number of frailty phenotype criteria seems to be associated with a decline in functional independence and in health-related quality-of-life.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A written informed consent was obtained from all individual participants included in the study.

Funding: The HIPFRA study is funded by the South Karelia Social and Health Care District (Eksote, register number 1236/00.01.05.01/2013), by two governmental funding sources; The Social Insurance Institution of Finland (SII, register number 94/331/2013) and State Research Funding for Academic Health Research (Ministry of Social Affairs and Health), and by the Vyborg Foundation Against Tuberculosis. The funding bodies had no role in the design of the study, in collection, analysis and interpretation of the data, or in writing the manuscript.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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II

EFFECTS OF HOME-BASED PHYSICAL EXERCISE ON DAYS AT HOME AND COST-EFFECTIVENESS IN PRE-FRAIL AND FRAIL PERSONS: RANDOMIZED CONTROLLED TRIAL

by

Suikkanen, S.A., Soukkio, P.K., Aartolahti, E.M., Kautiainen, H., Kääriä, S.M., Hupli, M.T., Sipilä, S., Pitkälä, K.H., Kukkonen-Harjula, K.T. 2021

Journal of the American Medical Directors Association 22(4):773-779

https://doi.org/10.1016/j.jamda.2020.06.005

JAMDA 22 (2021) 773–779

JAMDA

journal homepage: www.jamda.com

Original Study

Effects of Home-Based Physical Exercise on Days at Home and Cost-Effectiveness in Pre-Frail and Frail Persons: Randomized Controlled Trial

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Keywords:
Frailty
exercise
cost-effectiveness
utilization of social and healthcare services

A B S T R A C T

Objectives: Frailty increases the risks of hospitalization, institutionalization, and death. Our objective was to study the effects of home-based physical exercise on the number of days spent at home among pre-frail and frail persons, versus usual care. In addition, utilization and costs of health care and social services, cost-effectiveness, and health-related quality-of-life (HRQoL) were explored.
Design: Randomized controlled trial, with year-long supervised exercise for 60 minutes twice a week versus usual care. Follow-up for 24 months after randomization.
Setting and Participants: A sample of 299 home-dwelling persons in South Karelia, Finland. Main inclusion criteria: ≥65 years, meeting at least 1 of the frailty phenotype criteria, Mini-Mental State Examination score ≥17.
Methods: Primary outcome, days spent at home over 24 months, was calculated deducting days in inpatient care, in nursing homes, and days after death. HRQoL was assessed (15D questionnaire) at baseline and at 3, 6, and 12 months. Utilization data were retrieved from medical records.
Results: The participants' mean age was 82.5 (SD 6.3), 75% were women, 61% were pre-frail and 39% frail. After 24 months, there was no difference between groups in days spent at home [incidence rate ratio 1.03; 95% confidence interval (CI) 0.98–1.09]. After 12 months, the costs per person-year were 1.60-fold in the exercise group (95% CI 1.23–1.98), and after 24 months, 1.23-fold (95% CI 0.95–1.50) versus usual care. Over 12 months, the exercise group gained 0.04 quality-adjusted life-years and maintained the baseline 15D level, while the score in the usual care group deteriorated (*P* for group <.001, time 0.002, interaction 0.004).
Conclusions and Implications: Physical exercise did not increase the number of days spent at home. Exercise prevented deterioration of HRQoL, and in the frail subgroup, all intervention costs were compensated with decreased utilization of other health care and social services over 24 months.

The authors declare no conflicts of interest.
This work was supported by South Karelia Social and Health Care District (Eksote, grant register number 1236/00.01.05.01/2013); the Social Insurance Institution of Finland (SII, register number 94/331/2013); and State Research Funding for Academic Health Research (Ministry of Social Affairs and Health, Finland). The funders had no role in the design, or in collection, analysis, and interpretation of the data, or in writing the manuscript.
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https://doi.org/10.1016/j.jamda.2020.06.005
1525-8610/

Frailty is a medical condition caused by deterioration of the physiological capacity of the organ systems, predisposing a person to stressors such as infections.[1–3] Recovery from illnesses is slow, and the person may not recuperate to their previous functional level.[1] Frailty is an extreme consequence of the normal aging process, being multidimensional and dynamic,[4,5] and is more prevalent in women than in men.[6,7] Physical frailty is defined by frailty phenotype criteria, which include weight loss, weakness, low physical activity, slowness, and exhaustion.[8] By meeting 3 or more of the criteria, a person is considered as frail and by meeting 1 or 2, as pre-frail.[8]

When compared with robust persons, frail persons experience more hospitalizations[9–12] and longer stays at hospital;[13] they have lower health-related quality-of-life (HRQoL)[14] and a higher risk of mortality.[2,15] Both frailty and pre-frailty states are predictors of nursing home placement.[16] The severity of frailty is associated with greater health care and social services costs, as they can be 2.6 times higher for frail persons, and 1.7 times higher for pre-frail persons when compared with robust persons.[17,18]

Treatment of frailty is nonpharmacological, and progressive, individualized multicomponent physical exercise with resistance training is 1 option.[3] Whether exercise regimens can decrease inpatient hospital stays and postpone nursing home admission, and whether the period of living at home could thus be lengthened, are open questions when considering frail and pre-frail older adults. Furthermore, there is a scarcity of studies on home-based training,[3] and there is inconsistent evidence on whether or not physical exercise can improve HRQoL among frail and pre-frail older adults[19,20] and whether exercise interventions are cost-effective.

The primary aim of this randomized controlled trial was to study the effects of a 12-month physiotherapist-supervised home-based physical exercise program on the number of days spent at home over 24 months in pre-frail and frail persons, compared with usual care. In addition, the utilization and costs of health care and social services over 24 months, and HRQoL over 12 months were assessed. We also calculated quality-adjusted life-years (QALYs) and cost-effectiveness of the intervention by using incremental cost-effectiveness ratio (ICER).

Methods

Design and Settings

The methods and protocol of this randomized controlled trial have been previously presented in detail.[21] A total of 300 voluntary participants were recruited between December 2014 and August 2016. Before the start of recruitment, the study was registered at ClinicalTrials.gov (NCT02305433), and ethics approval was received in November 2014 from the relevant coordinating ethics committee. All participants signed a written informed consent document.

Participants

To be eligible, a person needed to score at least 1 point in the FRAIL questionnaire[22] and fulfill at least 1 of the frailty phenotype criteria.[8] Two of the phenotype criteria were slightly modified.[23] To define "low physical activity," we used 30 minutes per week as a cutoff value. For the slowness criterion, we used a common gait speed cutoff value of 0.46 m/s for both genders, which was based on the lowest quartile in the Short Physical Performance Battery.[24,25] Participants were classified as pre-frail if they met 1 to 2 phenotype criteria and frail if they met 3 to 5. Other eligibility criteria were as follows: age ≥65 years, home-dwelling (with or without homecare services), able to walk with or without aid when indoors, a Mini-Mental State Examination (MMSE)[26] score of ≥17, and no severe illnesses that prevented them taking part in exercise training. Eligible persons were randomized to physical exercise (n = 150) and usual care groups (n = 150). Randomization was performed after the baseline assessments in consecutive order by using a computer program with varying block sizes, without stratification.

Outcomes

The primary outcome was the number of days spent at home during the 24-month period (730 days), beginning at the date of randomization. The outcome was considered relevant as the national policy in our country is focused on supporting the older people's abilities to live at home, and postponing a possible nursing home placement. Overnight stays in hospital wards, long-term wards, nursing homes, and days after death up to the end of the 2-year period were summed up, and defined as days not lived at home. Information was gathered from the medical records of the social and health care district, which is responsible for primary and secondary health care and social services.

For secondary outcomes, data on the utilization and costs of health care and social services were gathered and analyzed over the 24-month period starting from the day of randomization. Business intelligence analysts, blinded to allocation, retrieved information on used services from the participants' medical records. We also retrieved information from the social insurance registers, which provided information on the number of used health care services in the private sector. Both datasets were merged by our statistician and included in our analyses.

All contacts between the patients and professionals in health care and social services, days in inpatient care and nursing homes, and the physiotherapy sessions of our intervention were included in the analyses. Costs were calculated by multiplying the number of service-utilization units by the price of each unit. National mean unit costs in 2011 were used,[27] and the prices were corrected to the 2018 level according to the inflation rate based on the cost-of-living index. For our intervention, the mean cost of 1 physiotherapist visit [86.50 euros (€)] was used and multiplied by the number of completed visits, and was included in the rehabilitation costs of the exercise group. Used services and costs are calculated per person-year, and all costs are presented in euros (€).

HRQoL was assessed via the 15D questionnaire[28] at baseline and after 3, 6, and 12 months. 15D has 15 items, each having 5 answer options. The questionnaire was sent to the participants before the assessor's home visits. Each person completed the questionnaire by themselves or with the help of relatives. If needed, the research physiotherapist or nurse helped the participant to complete the form. A weighted HRQoL index ranging from 1 (full health) to 0 (death) was calculated.

Cost-effectiveness of the intervention was assessed with ICER, based on the 12-month data of total costs (€) of used health care and social services and changes in QALYs.

At baseline, background information on marital status, living arrangements, illnesses, and medication were gathered by interview and were completed by using electronic medical records.

Intervention

Participants in the physical exercise group performed physiotherapist-supervised home-based physical exercises for 60 minutes, twice a week over 12 months. Exercises included 10 minutes of warm-up; 30 to 40 minutes of strength exercises mainly for the lower limbs; and 10 minutes of balance, flexibility, and functional exercises combined with other exercises. The physiotherapists tailored the exercises according to the participants' health status and condition. The main strength and balance exercises were based on the exercises of the Otago program.[29,30] Ankle weights, weight vests, dumbbells, kettlebells, and elastic bands were used to add resistance. Over the 12 months, exercise periods of power, force, and endurance were cycled every 8 to 12 weeks.

Therapists used dynamic, static, and dual-task exercises, different surfaces at home, and various types of equipment to add difficulty to the balance exercises. The goal was to include balance exercises as part of the functional exercises used to aid everyday tasks that a person needs to be able to live independently at home. Flexibility exercises were predominantly targeted at the larger joints to improve range of motion. Physiotherapists also gave counseling on nutrition. The participants could use all health care or social services they may have needed over 24 months. The usual care group continued to live their lives as usual, without restrictions.

Statistical Analysis

Concerning power calculations in connection with frail patients, there were no previous data on the duration of living at home. Therefore, we used data on Finnish patients with hip fractures in the PERFECT (PERFormance, Effectiveness and Cost of Treatment episodes) study,[31] in which data are available on the proportion of patients living at home 1 year after the fracture. To detect a difference ($\alpha = 0.05$, power = 80%) from the hypothesized difference of 180 days between the physical exercise and usual care groups, a sample size of 91 persons in each group would be needed. To allow for discontinuation (estimated as 15%) and death (20%) of participants during 24 months, our targeted sample size was 300 participants.

Descriptive statistics are presented as means with SDs or as counts with percentages. The primary outcome (days spent at home), and outpatient and inpatient visits to health care and social services were analyzed by using Poisson's model and reported as days and incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Repeated measures in HRQoL between the groups were analyzed by using mixed-effects models, with unstructured covariance structure (Kenward–Roger method to the calculate degrees of freedom). Fixed effects were group, time, and group-time interactions. Cost analyses were performed using a generalized linear regression model with log link and gamma variance functions. The variance function was selected based on the Park test and Akaike's information criterion.

Cost-utility analyses in relation to QALYs were based on areas under the curve of 15D scores from baseline to the last measurement point. All participants who completed the baseline assessment and had at least 1 other measurement point were included in the analyses of HRQoL and QALYs. All costs were presented per person-year. The cost-effectiveness of home-based physical exercise was compared with usual care by using ICER. The bootstrapping technique was used in connection with incremental cost-effectiveness planes for costs and QALYs (5000 replicates). The normality of variables was evaluated graphically and by using the Shapiro–Wilk W-test. Statistical analyses were performed by using the Stata 16.0, StataCorp LP (College Station, TX) statistical package.

Results

Eligibility was tested in 520 persons and recruitment was completed when the targeted 300 persons were reached. After randomization, 1 person in the usual care group withdrew his or her consent to participate and declined the use of his or her data. The flowchart is shown in Figure 1. The mean age of the 299 participants was 82.5 years, 75% were women, 39% were frail, 61% were pre-frail, and 58% lived alone. Baseline characteristics are shown in Table 1.

Primary Outcome

At 24 months, the primary outcome was analyzed in 299 participants. Over the 24 months (730 days), the mean number of days spent at home was 659 (95% CI 635–683) in the exercise group and 638 (95% CI 611–665) in the usual care group (IRR 1.03; 95% CI 0.98–1.09; $P = .26$). In addition, there was no difference in the days at home between the exercise and usual care groups by the frailty subgroups, for frail IRR 1.04 (0.96–1.12) and pre-frail IRR 1.03 (0.96–1.11). Eleven persons (7%) in the exercise group and 13 persons (9%) in usual care were permanently placed in nursing homes ($P = .66$). In the exercise group, 18 persons, and in usual care, 19 persons, died within the 24-month study period; of these, 5 and 10 persons died during the first 12 months, respectively (Figure 1). Sixty-one persons (41%) in the exercise group and 57 persons (38%) in usual care lived at home for the full 730 days without temporary inpatient care.

Secondary Outcomes

Data on utilization of health care and social services (outpatient visits and inpatient days) and related costs are presented in Table 2. Mean total costs incurred by health care and social services per person-year during the first 12 months were 1.60-fold (95% CI 1.23–1.98) in the exercise group (33,839 €) when compared with those in usual care (21,115 €). Over the 24-month period, mean costs per person-year were 1.23-fold (95% CI 0.95–1.50) in the exercise group (29,428 €) compared with those in usual care (23,961 €). Over the 24 months, in the exercise frail subgroup, the mean costs were 1.02 times (95% CI 0.75–1.38) higher (32,507€ [SE 3625] vs 31,979€ [SE 3597]) and in the exercise pre-frail subgroup 1.46 times (95% CI 1.03–2.06) higher (27,431 € [SE 3348] vs 18,851€ [SE 2301]) when compared with the corresponding subgroups in the usual care.

We analyzed the effects of the intervention on HRQoL over 12 months, covering 96% (n = 144) of the participants in the exercise group and 95% (n = 141) of those in usual care. In the usual care group, the mean HRQoL score decreased significantly by 0.037 compared with the exercise group, which maintained the baseline level (P for group <.001, time $P = .002$, interaction $P = .002$) (Figure 2). The difference in HRQoL is also seen in the subgroups of frail (P for group 0.002, time $P = .001$, interaction $P = .084$) and pre-frail (P for group 0.064, time $P = .078$, interaction $P = .004$) (Figure 2).

When HRQoL was converted to QALYs, the exercise group gained 0.040 QALYs more compared with the usual care group over the 12 months (mean QALYs 0.723 and 0.683, respectively). In the ICER plane, all participants lay in the northeast quadrant, implying that the intervention was more effective but more costly than usual care.

The intervention group completed in total 12,981 physical exercise sessions and the mean number of sessions per participant was 87, median 96, with range of 3 to 104. Of the participants, 58% reported exercise-related mild transient muscle soreness, and 71% reported mild joint pain at some point during the year; 17 falls occurred during exercise sessions, with 1 fall leading to an injury that needed medical care, and 18 persons took nitroglycerin during or after 1 exercise session. On 5 occasions, a participant needed acute medical care because of health problems at the time of the physiotherapist visit.

Discussion

The primary aim of this trial was to explore the effects of a 12-month supervised home-based physical exercise regimen on the number of days lived at home among pre-frail and frail persons within 24 months. Our intervention did not significantly increase the number of days spent at home compared with usual care.

In previous studies, interventions including exercise training have not decreased the rates of permanent nursing home placements or

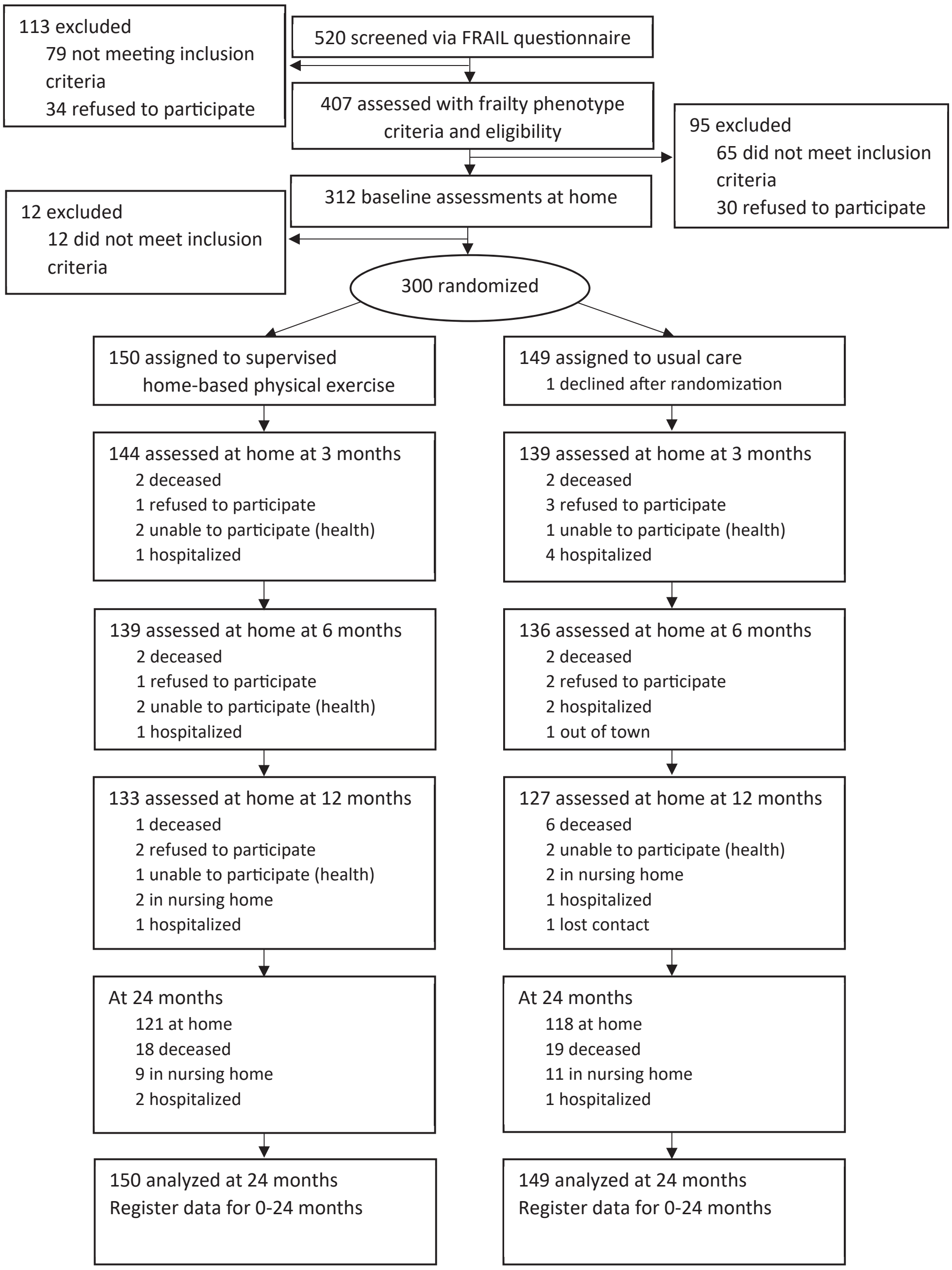

Fig. 1. Flowchart of the randomized controlled trial; number of participants.

acute hospitalizations in community-living frail persons,[32] or hospitalizations in persons living in nursing homes.[33] Frail persons are at a higher risk of nursing home placement than pre-frail persons, and pre-frail persons are at a higher risk when compared with robust persons.[34] In our trial, most participants were pre-frail (61%), which might reflect the low number of persons transferred to nursing homes. In addition, there was no difference between the groups in the 24-month mortality rate.

Our secondary aim was to study if costs of health care and social services can be reduced by way of the physical exercise regimen. Frailty is associated with higher rates of hospitalization,[35] longer hospital stays,[13] and higher health care costs,[36] and clinical guidelines recommend physical exercise as a treatment option for frailty.[3] Over intervention year the costs per person-year in the exercise group were found to be increased versus usual care, but the difference decreased over the next 12 months. The total costs over 24 months in the frail subgroup were the same between the exercise and usual care, but the pre-frail exercise subgroup remained higher versus usual care. Thus, targeting the intervention to those who are frail seems to be the most cost-beneficial. In another study, an intervention with physical exercise was considered as the most likely cost saving among the very frail.[37]

Over the 12-month intervention period, those in the exercise group maintained their HRQoL score at the baseline level, whereas the score

Table 1
Baseline Characteristics of Participants in the Physical Exercise and Usual Care Groups

Characteristics	Physical Exercise (n = 150)	Usual Care (n = 149)	*P* Value
Age, mean (SD)	82.2 (6.3)	82.7 (6.3)	.44
Women, n (%)	114 (76)	110 (74)	.67
Body mass index (kg/m^2), mean (SD)	28.4 (5.5)	28.6 (6.1)	.78
MMSE,* mean (SD)	24.2 (3.1)	24.6 (3.2)	.39
Marital status, n (%)			.19
Married/in a relationship	56 (37)	62 (42)	
Single/divorced	19 (13)	27 (18)	
Widowed	75 (50)	60 (40)	
Living, n (%)			.13
Alone	88 (59)	86 (58)	
With spouse	47 (31)	57 (38)	
With another person (other than spouse)	15 (10)	6 (4)	
Home care at least once a week, n (%)	27 (18)	34 (23)	.30
Education <9 years, n (%)	99 (66)	90 (60)	.32
Severity of frailty			.94
Pre-frail, 1–2 of the 5 criteria, n (%)	91 (61)	91 (61)	
Frail, 3–5 of the 5 criteria, n (%)	59 (39)	58 (39)	
Physician-diagnosed diseases or disorders, n (%)			
Cardiovascular diseases*	76 (52)	91 (61)	.070
Hypertension	110 (73)	110 (74)	.92
Stroke or TIA	37 (25)	33 (22)	.61
Diabetes	31 (21)	45 (30)	.059
Musculoskeletal diseases	129 (86)	124 (83)	.51
COPD or asthma	16 (11)	20 (13)	.46
Dementia	19 (13)	22 (15)	.60
Number of regular medications, mean (SD)	6.7 (3.2)	7.0 (3.1)	.43
HRQoL, 15D, mean (SD)	0.719 (0.084)	0.705 (0.097)	.19

COPD, chronic obstructive pulmonary disease; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack.
Means (SD) or proportions (%).
*Includes coronary heart disease, angina pectoris, myocardial infarction, heart failure.

Table 2
Use of Health Care and Social Services (Outpatient Visits to Health Care, Inpatient Days in Hospitals and Nursing Homes, and Home Care Visits) and Their Costs (€) Per Person-Year in the Physical Exercise and Usual Care Groups Over 0 to 12 Months and 0 to 24 Months

	Health Care and Social Services, Visits or Days Per Person-Year			Health Care and Social Services, Costs Per Person-Year		
	Usual Care (n = 149)	Physical Exercise (n = 150)	IRR* (95% CI)	Usual Care (n = 149)	Physical Exercise (n = 150)	Mean Ratio† (95% CI)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean, € (SE)	Mean, € (SE)	Mean, € (SE)
0–12 mo						
Home care, visits	160.5 (24.8)	117.2 (19.3)	0.73 (0.47–1.14)	7187 (1093)	5269 (866)	0.73 (0.41–1.05)
Primary care						
General practitioner, visits	9.57 (0.70)	9.41 (0.74)	0.98 (0.80–1.21)	1234 (114)	1201 (114)	0.97 (0.72–1.23)
Nurse, visits	19.56 (1.60)	17.19 (1.41)	0.88 (0.70–1.10)	1023 (83)	907 (76)	0.89 (0.69–1.09)
Rehabilitation,‡ visits	8.06 (1.09)	91.54 (1.50)	11.35 (8.69–14.82)	1407 (187)	8153 (145)	5.79 (4.28–7.30)
Primary care ward, days	8.03 (2.74)	6.29 (1.72)	0.78 (0.33–1.85)	2750 (867)	2468 (708)	0.90 (0.15–1.64)
Home health care, visits	2.98 (0.50)	2.99 (0.52)	1.00 (0.63–1.61)	373 (63)	389 (69)	1.04 (0.54–1.54)
Specialized medical care						
Physician, visits	2.50 (0.28)	2.29 (0.28)	0.92 (0.66–1.26)	694 (77)	668 (82)	0.96 (0.65–1.27)
Nurse, visits	1.30 (0.32)	1.38 (0.34)	1.07 (0.54–2.10)	66 (16)	72 (18)	1.11 (0.38–1.83)
Emergency department, visits	1.73 (0.23)	1.84 (0.23)	1.06 (0.74–1.52)	590 (80)	683 (116)	1.16 (0.66–1.65)
Hospital wards, d	3.26 (0.49)	4.57 (0.80)	1.40 (0.89–2.21)	3644 (831)	4931 (1175)	1.35 (0.48–2.22)
Nursing home, d	3.04 (1.15)	5.20 (2.09)	1.71 (0.58–5.04)	777 (360)	946 (372)	1.22 (0.24–2.67)
Total costs				21,151 (2185)	33,839 (2167)	1.60 (1.23–1.98)
0–24 mo						
Home care, visits	185.2 (27.1)	141.2 (22.6)	0.76 (0.50–1.17)	8268 (1162)	6475 (1000)	0.78 (0.47–1.10)
Primary care						
General practitioner, visits	10.65 (0.68)	9.82 (0.70)	0.92 (0.77–1.11)	1387 (112)	1289 (113)	0.93 (0.71–1.15)
Nurse, visits	20.53 (1.60)	18.32 (1.31)	0.89 (0.72–1.10)	1067 (81)	963 (72)	0.90 (0.71–1.09)
Rehabilitation,‡ visits	7.78 (0.84)	50.34 (1.07)	6.47 (5.21–8.04)	1347 (152)	4847 (155)	3.60 (2.78–4.42)
Primary care ward, d	9.70 (2.60)	6.56 (1.47)	0.68 (0.34–1.34)	3378 (834)	2880 (712)	0.85 (0.26–1.44)
Home health care, visits	3.06 (0.41)	3.19 (0.45)	1.04 (0.71–1.53)	400 (56)	427 (64)	1.07 (0.64–1.49)
Specialized medical care						
Physician, visits	2.40 (0.23)	2.35 (0.25)	0.98 (0.74–1.30)	669 (65)	706 (77)	1.06 (0.76–1.35)
Nurse, visits	1.37 (0.23)	1.53 (0.32)	1.12 (0.66–1.90)	71 (12)	82 (17)	1.16 (0.55–1.77)
Emergency department, visits	1.53 (0.18)	1.81 (0.19)	1.18 (0.87–1.61)	578 (72)	724 (113)	1.25 (0.76–1.75)
Hospital wards, d	3.20 (0.41)	4.22 (0.58)	1.32 (0.91–1.91)	3956 (819)	5064 (1137)	1.28 (0.53–2.03)
Nursing home, d	7.14 (1.99)	6.48 (2.44)	0.91 (0.36–2.27)	1554 (460)	1240 (431)	0.80 (0.09–1.51)
Total costs				23,961 (2198)	29,428 (2282)	1.23 (0.95–1.50)

*Incidence rate ratio, the physical exercise group over the usual care group.
†Mean ratio, the physical exercise group over the usual care group.
‡Including physiotherapy, occupational therapy, speech therapy, and trial intervention (physiotherapist-supervised home-based physical exercise).

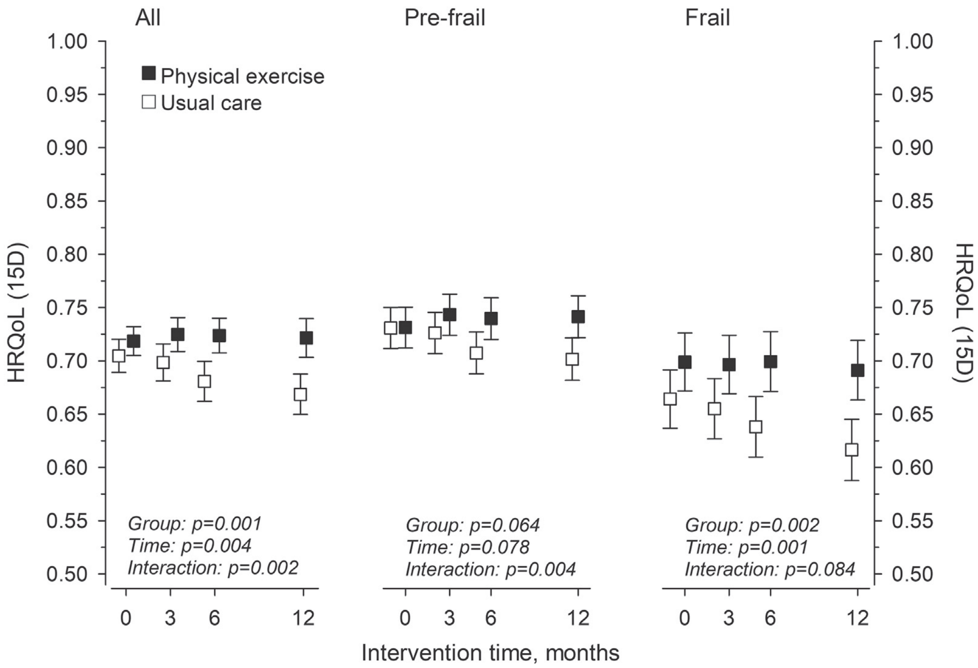

Fig. 2. HRQoL in the physical exercise group and the usual care groups, in all participants and in subpopulations of pre-frail and frail over the 12-month intervention period. Means with whiskers representing 95% CI.

in the usual care group deteriorated by 0.037. This deterioration can be considered as considerable and clinically meaningful. Regarding the 15D measure, a minimal important change has been proposed to be ±0.015 and a change of ±0.035 can be considered large.[38] In health care interventions, physical exercise has had an inconclusive effect on HRQoL in pre-frail and frail older adults,[20] and HRQoL did not change in previous short-term home-based training studies.[39,40]

From the cost-effectiveness point of view, exercise was more effective and more costly within the first 12 months, as the exercise group gained 0.04 QALYs more and the costs were 1.60-fold greater compared with the usual care group. Our findings are in line with those in the LIFE study, in which sedentary older persons who participated in physical activity with a goal of 150 minutes per week accrued 0.047 QALYs over 2.6 years compared with the group that received health education.[41] In comparison with our study, not all the participants in the LIFE study[41] were frail at the beginning, as it was not among the inclusion criteria.

As a strength of our trial, it had a rigorous randomized design. All 299 participants were followed using register data for 24 months, or until their death. We retrieved data from medical records and were able to identify every contact between a patient and health care and home care professionals, which took place in the services provided by the district. We were also able to retrieve information on visits to private outpatient health care services from the social insurance registers, although the number of reimbursed visits was low. As a limitation of our trial, we assessed HRQoL and QALYs only for the first 12 months (as planned). In addition, during our study period (2014–2018), the policies in the district changed: resources were targeted more to services at home such as homecare, and the number of nursing homes was reduced. In 2018, the district had the lowest national percentage of older persons in nursing homes.[42] This development may also have had an impact on the total number of persons assigned to long-term care in our study. A longer follow-up time or including only frail participants might have had more impact on the between-group difference in the days at home. In future trials, finding a way to decrease the costs of the supervised home-based exercise intervention (eg, with the help of remote technologies), or combining exercise to homecare visits could be beneficial.

Conclusions and Implications

Contrary to our hypothesis, the 12 months' physiotherapist-supervised home-based physical exercise in frail and pre-frail persons had no effect on the number of days spent at home. The exercise investment was costly, but the costs were gained back in decreased utilization of health care and social services in the exercise frail subgroup over 24 months. Physical exercise had a considerable clinical effect on HRQoL and QALYs when compared with the usual care.

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III

EFFECT OF 12-MONTH SUPERVISED, HOME-BASED PHYSICAL EXERCISE ON FUNCTIONING AMONG PERSONS WITH SIGNS OF FRAILTY: A RANDOMIZED CONTROLLED TRIAL

by

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Archive of the Physical and Medical Rehabilitation 102(12):2283-2290

https://doi.org/10.1016/j.apmr.2021.06.017

ACRM AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2021;000: 1−8

ORIGINAL RESEARCH

Effect of 12-Month Supervised, Home-Based Physical Exercise on Functioning Among Persons With Signs of Frailty: A Randomized Controlled Trial

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Abstract

Objectives: To investigate the effects of a 12-month home-based exercise program on functioning and falls among persons with signs of frailty.

Design: A randomized controlled trial with a 1:1 allocation.

Setting: Home-based.

Participants: Home-dwelling persons aged 65 years or older meeting at least 1 frailty phenotype criteria (N=300). The mean age of the participants was 82.2±6.3 years, 75% were women, 61% met 1-2 frailty criteria, and 39% met ≥3 criteria.

Interventions: A 12-month, individually tailored, progressive, and physiotherapist-supervised physical exercise twice a week (n=150) vs usual care (n=149).

Main Outcome Measures: FIM, Short Physical Performance Battery (SPPB), handgrip strength, instrumental activities of daily living (IADL), and self-reported falls and physical activity (other than intervention). Assessed 4 times at home over 12 months.

Results: FIM deteriorated in both groups over 12 months, −4.1 points (95% confidence interval [CI], −5.6 to −2.5) in the exercise group and −6.9 (95% CI, −8.4 to −2.3) in the usual care group (group *P*=.014, time *P*<.001, interaction *P*=.56). The mean improvement in SPPB was significantly greater in the exercise group (1.6 [95% CI, 1.3-2.0]) than in the usual care group (0.01 [95% CI, −0.3 to 0.3]) (group *P*<.001, time *P*=.11, interaction *P*=.027). The exercise group reported significantly fewer falls per person-year than the usual care group (incidence rate ratio, 0.47 [95% CI, 0.40-0.55]; *P*<.001). There was no significant difference between the groups over 12 months in terms of handgrip strength, IADL function, or self-reported physical activity.

Conclusions: One year of physical exercise improved physical performance and decreased the number of falls among people with signs of frailty. FIM differed between the groups at 12 months, but exercise did not prevent deterioration of FIM, IADL, or handgrip strength.

Archives of Physical Medicine and Rehabilitation 2021;000:1−8

Frailty is a syndrome that occurs especially in older adults[1] and is often associated with sarcopenia.[2] People with frailty often have impaired functioning as well as diminished muscle strength and endurance,[3,4] and frailty increase the risk of disability and falls.[5] Physical frailty can be defined via 5 phenotypic criteria: weight loss, weakness, slowness, low physical activity, and exhaustion.[6]

Presented as a poster to the International Association of Geriatrics and Gerontology-European Region Congress, May 25, 2019, Gothenburg, Sweden; presented to the European Geriatric Medicine Society, September 27, 2019, Krakow, Poland.

Supported by the South Karelia Social and Health Care District (Eksote; register no. 1236/00.01.05.01/2013), the Social Insurance Institution of Finland (SII; register no. 94/331/2013), and the Finland State Research Funding for Academic Health Research (Ministry of Social Affairs and Health). The funders played no role in the design, collection, analysis, or interpretation of the data, nor in writing the manuscript.

Clinical Trial Registration No.: NCT02305433.

Disclosures: none

0003-9993/$36 - see front matter
https://doi.org/10.1016/j.apmr.2021.06.017

Physical exercise is a promising treatment option for frailty.[3,7,8] Group-based exercise training for frail older adults has shown positive effects on physical performance,[9,10] and physical activity can postpone harmful consequences[8] such as disabilities, falls, and mortality.[3,4,6] The strongest evidence comes from multicomponent training programs with resistance training as the central component, accompanied by aerobic, balance, and flexibility exercises.[8,11]

Even though physical exercise is a treatment option for frailty, persons with signs of frailty may think that they lack the capacity to be physically active.[12] The barrier to participate in physical activities may be lowered by providing opportunities for instructed exercise near their own homes.[12] Supervised home-based training might be a valuable option for frail older adults, but evidence on its effectiveness is still scarce. Previous home-based exercise trials targeting frail older adults have consisted of interventions of a maximum of 6 months with limited supervision from professionals and inconclusive results.[13]

The aim of this randomized trial was to investigate the effects of a 12-month physiotherapist-supervised, home-based exercise program on functioning and falls among people with signs of frailty compared with usual care.

Methods

Study design

This article reports secondary outcomes of our trial, which was registered to ClinicalTrials.gov (NCT02305433) before recruitment. The study protocol has been published,[14] and the primary outcome, days lived at home, has been reported earlier.[15] In short, we performed a parallel, randomized controlled trial with a 1:1 allocation ratio. After the baseline assessments, the research personnel randomized participants into 2 groups, using a computer-generated random sequence allocation program with randomly varying block sizes from 2-10, without stratification. A statistician, who had no role in the trial, created the randomization program. One person in the research group used the randomization program and informed the participants of their allocation by phone. The allocation groups were a physiotherapist-supervised physical exercise group (n=150) and a usual care group (n=150).

Participants

Home-dwelling individuals aged ≥65 years were recruited between December 2014 and August 2016, via advertisements in newspapers and with the help of the home health care personnel of the social and health care district. To be eligible, the individuals needed to pass through a 2-phase recruitment process and had to fulfill at least 1 phenotype criterion of frailty. First, they were evaluated using the Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight (FRAIL) questionnaire.[16,17] FRAIL has 5 domains with 1 point each: Fatigue (feeling tired all the time or most of the time), Resistance (unable to climb 1 flight of stairs), Ambulation (unable to walk 1 block), Illnesses (>5), and Loss of Weight (>5% during the previous year). If a person scored at least 1 point in FRAIL they advanced to the second phase, where the research nurse checked their eligibility criteria and verified their frailty status using the phenotype criteria of Fried et al[6] with slight modifications. The criteria used were weight loss ≥5% during the preceding year,[6] physical activity <30 min/wk,[18] a feeling of "not getting going" or "everything is an effort" for most or all of the time,[6] handgrip strength under cutoff values based on body mass index and sex,[6] and walking speed <0.46 m/s (walking length either 4 or 2.44m).[19]

Other eligibility criteria were residing at home, ability to walk indoors with or without mobility aids, scoring ≥17 on the Mini-Mental State Examination,[20] and ability to communicate in Finnish. Individuals were excluded if they were living in an institutional care facility or nursing home, had alcohol or drug abuse problems, had severe problems with hearing or eyesight, had terminal illnesses (eg, cancers), or had other severe illnesses (eg, a cardiovascular disease with New York Heart Association Functional Classification class III or IV, severe pulmonary disease, stroke) that was contraindication to physical exercise. The study received ethics approval on November 12, 2014, from the Coordinating Ethics Committee and was conducted in accordance with the standards of the Declaration of Helsinki. All the participants were volunteers and signed a written informed consent document prior to the baseline assessments.

List of abbreviations:

CI	**confidence interval**
FRAIL	**Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight**
IADL	**instrumental activities of daily living**
IQR	**interquartile range**
SPPB	**Short Physical Performance Battery**

Outcomes

Here we report the secondary outcomes of our trial. A research physiotherapist/nurse not blinded to the allocation performed assessments at the participant's home using interviews, questionnaires, and measurements at baseline and at 3, 6, and 12 months. If necessary, details of demographic characteristics and illnesses were complemented with electronic medical records of the social and health care district. The assessors did not participate in the implementation of the intervention.

Functioning was assessed using several measurements. The FIM[21] evaluates the participant's ability to perform 13 motor and 5 cognition tasks and was performed via an interview. Each task was graded on a scale of 7 (fully independent) to 1 (needs assistance from 2 people). Maximum points were 126: 91 for motor and 35 for cognition. Instrumental activities of daily living (IADL) were assessed via Lawton's 8-item questionnaire,[22] using polytomous item scoring (1-3, 1-4, or 1-5), with higher scores indicating better functioning and an item sum ranging from 8-31.[23] Physical performance was assessed using the Short Physical Performance Battery (SPPB),[19] which has 3 parts (balance, walking, chair rise test) and a maximum summary score of 12 points. Handgrip strength was measured in seated position, 3 times from both hands using a handheld dynamometer,[a] the elbow unsupported in a 90-degree angle, placed next to the body, and the wrist in a neutral position.[24] The mean of the best values of both hands was used in the analyses to eliminate possible joint conditions in 1 hand that would hinder the maximal performance. Frequency of physical activity (intervention physical exercise not included) was assessed by 2 structured questions[25] during the interviews: (1) how often did you have a walk outdoors at least 30 minutes at a time in the previous month and (2) how often did you perform physical activities other than walking at least 30 minutes at a time in the previous month. Physical activity was reported as weekly sessions, which was calculated by summing up the number of sessions from both questions.

Falls were queried during the assessment visits as participants reported the number of all falls during the previous 3 or 6 months.

Physical exercise intervention

The 12-month exercise program comprised physiotherapist-supervised, 1-hour sessions twice a week at the participant's home. The research group trained the physiotherapists to conduct a structured, periodical, progressive, and multicomponent physical exercise program, which included strength, balance, mobility, and functional exercises (table 1).[14] The physiotherapists modified the sessions to suit the participants' current health status. The physiotherapists were instructed to periodically perform multiple-repetition maximum tests for lower extremities with ankle weights (0.5-10kg) to ensure progression and define suitable training resistance. At the end of each session, its intensity was evaluated with Borg's ratings of perceived exertion scale,[27] with the targeted range from moderate (12) to vigorous (17), and the intensity of the following session was modified accordingly. The physiotherapist also gave brief counseling on nutrition and encouraged the participant to be physically active outside the supervised exercise sessions. The physiotherapists reported contents of all the exercise sessions and adverse effects monthly. In addition, the participants could receive any social and health care (including rehabilitation) services they needed during the trial.

Usual care

In the usual care group, the participants continued to live their lives "as usual." They received any health care or social services they needed during the study period, including home care and rehabilitation delivered according to the social and health care district's normal policies.

Statistical analysis

The sample sizes were calculated in proportion to the primary outcome, which was number of days living at home over 24 months. In brief, to detect a difference (α [significance level]=0.05, β [power]=80%) of the hypothesized 180±431 days between the physical exercise and usual care groups, a sample size of 91 persons in each group would have been needed (simulation-based effect size was 0.40). To allow for discontinuation (estimated as 15%) and death (20%) of participants, our targeted sample size was 300 participants. More detailed description of power calculations is reported elsewhere.[14,15]

All analyses were performed based on the intention-to-treat principle. The characteristics of the participants are reported as means with SDs, as medians with interquartile ranges (IQRs), or as counts with percentages. Repeated measurements taken at different assessment points were analyzed using mixed-effects models with an unstructured covariance structure (Kenward-Roger method to calculate the degrees of freedom). The fixed effects were group, time, and group-time interaction. Mixed models allowed analyses of unbalanced data sets without imputation; therefore, all available data were analyzed with the full analysis set. The Benjamini-Hochberg step-up false discovery rate[29] was applied to correct the levels of significance for multiple testing in the single FIM items. Poisson regression was used to calculate the incidence rate ratio for falls. The Poisson regression model was tested using the goodness-of-fit test of the model, the assumptions of over dispersion in the Poisson model were tested using the Lagrange multiplier test, and overdispersion was not detected. Normal distributions were evaluated graphically and using the Shapiro-Wilk W test. Stata 16.1[b] was used for the analyses.

Results

At baseline, the mean age was 82.2±6.3 years in the exercise group and 82.7±6.3 in the usual care group. Most of the participants were female (75%), 61% met 1-2 frailty criteria and 39% met ≥3, and 80% of the participants used walking aids (table 2). Soon after randomization, 1 participant withdrew and refused use of their data, decreasing the number of participants in the usual care group to 149. A total of 133 participants in the exercise group and 127 in the usual care group participated in the assessments at 12 months (fig 1).

In the exercise group, attendance of the home-based exercise sessions ranged from 3-104 with a median of 96 (IQR, 87-99). Participation rate >75% was achieved by 128 participants (85%). The median of other rehabilitation sessions (eg, physiotherapy, occupational therapy) received from the social and health care district during the intervention year was 0 (IQR, 0-2) in the exercise group and 1 (IQR, 0-8) in the usual care group.

In both groups, the mean FIM score deteriorated over the 12 months (group P=.014, time P<.001, interaction P=.56) (fig 2). Overall, in the exercise group the mean FIM score changed by −4.1 points (95% confidence interval [CI], −5.6 to −2.5), and in the usual care group it changed by −6.9 points (95% CI, −8.4 to −2.3). Compared with the 12-month change in single FIM motor items (fig 3), the exercise group performed better in transferring to the bath/shower (P=.037) and walking on stairs (P=.036) than the usual care group, after correcting the levels of significance for multiple testing.

In IADL the baseline mean scores were 23±5 in the exercise and 23±6 in the usual care group. Over 12 months IADL functions deteriorated in both groups; the mean change was −1.4 points (95% CI, −1.9 to −0.9) in the exercise group and −2.1 (95% CI, −2.6 to −1.6) in the usual care group (group P=.095, time P<.001, interaction P=.92).

In the SPPB, the mean improvement over 12 months was 1.6 (95% CI, 1.3-2.0) points in the exercise group and 0.01 (95% CI, −0.3 to 0.3) points in the usual care group (P<.001) (see fig 2). The mean change in handgrip strength was −0.5 kg (95% CI, −1.0 to 0.1) in the exercise group and −1.2 kg (95% CI, −1.7 to −0.6) in the usual care (group P=.26, time P<.001, interaction P=.29).

At baseline, the participants in the exercise group reported on average 2.2 (95% CI, 1.8-2.7) and in the usual care group 2.2 (95% CI, 1.8-2.6) weekly physical activity sessions lasting for at least 30 minutes at a time. At 6 months, the exercise group had increased the number of weekly sessions to 3.3 (95% CI, 2.7-4.0), and the usual care group had increased to 2.7 (95% CI, 2.2-3.2). At 12 months, the number of weekly sessions declined close to baseline level, to 2.5 (95% CI, 1.9-3.0) and 2.1 (95% CI, 1.7-2.5), respectively (group P=.26, time P<.001, interaction P=.32) (see fig 2).

During the intervention year, the participants in the exercise group had 1.4 (95% CI, 1.2-1.6) and the usual care group had 3.1

Table 1 Contents of one 60-minute physical exercise session, supervised by a physiotherapist

Variables	Warm-up Exercises	Resistance Training	Balance Training	Flexibility Training	Functional Exercises	Counseling
Duration	5-10 min	30-40 min	5-10 min	5-10 min	5-10 min	Individual
Main exercises	Walking, chair exercises, stationary cycling.	Focus on lower limbs, main exercises based on Otago program.[26] Exercises included, eg, knee extension, knee flexion, hip abduction, calf raises, toe raises. Upper limbs: no specific movements assigned.	Static, dynamic, and dual-task exercises based on Otago program,[26] eg, tandem stand, squats, walking in various directions.	Stretching, reaching.	Tasks of IADL, such as climbing stairs, washing dishes, handling laundry, piling firewood, walking outside, grocery shopping.	Nutrition: energy intake, protein intake, meal pattern, fluid intake. Physical activity counseling and encouragement.
Intensity	Low to moderate	Moderate to vigorous	Moderate	Low	Moderate to vigorous	Individual
RPE[27]	10-12	12-17	12-14	10-11	12-17	
Progression	Longer distance or more challenging terrain, or, eg, higher resistance in the stationary cycle.	Increasing the number of sets, repetitions, and resistance with ankle weights to match the targeted RPE and the phase of the training cycle: 1st mo getting used to exercises; 2nd-3rd mo strength (sets 2-5, reps 8-12, 60%-80% of maximum muscle strength according to multiple RM test[28]); 4th-6th mo power (sets 3-5, reps 4-10, 20%-60%); 7th-9th mo endurance (sets 2-3, reps. 12-30, 20%-60%); 10th-12th mo strength/power.	More challenging surfaces and tasks to challenge the participant's balance. Starting from static exercises, progressing to dynamic and dual-task exercises.	Larger range of motion.	Advancing to more challenging tasks and combined with strength and balance training.	From broad and general to the more specific.
Accessories	Walking aid (if needed), fitness equipment, eg, stationary bike	Resistance with ankle weights (0.5 kg-10 kg), dumbbells, kettlebells, rubber bands	Balance pads, different types of floor surfaces, outdoor environment	Stick	Natural home environment	Pamphlets and booklets
Goal	To warm up and prepare the body before other exercises	To increase the strength of lower limbs and to enhance physical performance	To challenge individual balance abilities, to prevent falls	To enlarge the range of motion in large joints to maintain ADL	To support individual abilities to live independently at home	To provide knowledge and motivate to follow nutrition and exercise guidelines

Abbreviations: ADL, activities of daily living; RM, repetition maximum; RPE, rating of perceived exertion; rep, repetition.

Table 2 Baseline characteristics of participants in physical exercise and usual care groups

Characteristic	Physical Exercise (n=150)	Usual Care (n=149)
Age (y), mean ± SD	82.2±6.3	82.7±6.3
Women, n (%)	114 (76)	110 (74)
No. of frailty criteria, n (%)*		
1	44 (29)	48 (32)
2	48 (32)	44 (30)
3	40 (27)	42 (28)
4	13 (9)	13 (9)
5	5 (3)	2 (1)
Mini-Mental State Examination, mean ± SD†	24.2±3.1	24.6±3.2
FIM, mean ± SD‡	109±10	109±11
IADL, mean ± SD§	23±5	23±6
SPPB, mean ± SD‖	6.1±2.7	6.3±2.5
Handgrip strength (kg), mean ± SD¶	18.9±7.8	19.7±7.8
Living alone, n (%)	88 (59)	86 (58)
Walking aids, n (%)	122 (81)	117 (79)
No. of regular medications, mean ± SD	6.7 (3.2)	7.0 (3.1)

* According to modified phenotype criteria of Fried et al.[6]
† Points range from 0-30, a higher value indicating better cognition.
‡ Points range from 18-126, a higher score indicating better functional independence.
§ Reported as an item sum, points range from 8-31, a higher score indicates better functioning.
‖ Scores range from 0-12, a higher score indicates better performance.
¶ Mean of best values of both hands.

(95% CI, 2.8-3.4) falls per person-year. The difference between the groups was significant (incidence rate ratio, 0.47 [95% CI, 0.40-0.55]; *P*<.001).

Discussion

Persons with signs of frailty who participated in a yearlong home-based physical exercise program improved their SPPB more, and they experienced fewer falls than those who received usual care. In both groups, FIM declined over 12 months. However, at 12 months, the physical exercise group had a significantly better FIM score than the usual care group, whereas there was no difference between the groups in handgrip strength or IADL functions. The frequency of self-reported physical activity sessions during leisure time increased in both groups until 6 months but reverted to baseline level at 12 months, with no significant difference between the groups.

Over 12 months, all motor and cognitive components of FIM deteriorated in both groups. The FIM evaluates a person's need for care in everyday tasks and has mainly been used in inpatient rehabilitation.[21] We assessed FIM by an interview at the person's home. Only a few other studies have used FIM in outpatient settings among older adults. In 2 Finnish studies, FIM was used to measure the change over 12 months among older people at risk of institutionalization (AGE study)[30] and people with Alzheimer disease (FINALEX study).[31] In both studies, FIM deteriorated in the intervention and usual care groups, as in our study, and among the people in the intervention groups, deterioration was slower. The AGE[30] and FINALEX[31] participants were on average a few years younger than those in our sample, and the FINALEX study used a home-based intervention[31] similar to ours. Some of our participants might have been unable to improve their FIM scores because of the aids they used at home (eg, dentures, walking aids, shower handles, raised beds, use of a banister), which they were unwilling or unable to discard.

Because SPPB predicts nursing home admissions[19] and all-cause mortality[32] and is a fast and easy way to measure physical performance, it is widely used in clinical practices. In our trial, SPPB improved in the exercise group by 1.6 points over 12 months, which can be considered clinically important. In previous studies a substantially clinical meaningful change in SPPB has been estimated to range from 0.4-1.5 points[33] and from 0.5-1.3 points.[34] In community-living older adults with frailty, group-based supervised exercise training of 24 weeks improved their SPPB score by 0.9 points, whereas that of the usual care group deteriorated by 1.5 points.[10] In all these studies[10,33-35] the participants had better baseline SPPB scores than ours. Among frail nursing home residents[36] with a similar SPPB baseline level to ours, a 6-month progressive multicomponent group-based exercise intervention improved the mean SPPB score by 1.8 points, whereas the mean score in the control group declined by 0.9 points.

Another important gain was the smaller number of falls in our exercise group than in the usual care group. We based our intervention on the exercises from the OTAGO exercise program, which effectively reduced the number of falls among community-dwelling older adults.[37] An Italian cross-sectional study on older outpatients in a geriatric clinic[38] found an association between lower SPPB scores and history of falls. In our trial, no severe complications occurred; only 1 injurious fall during exercise session needed medical care.

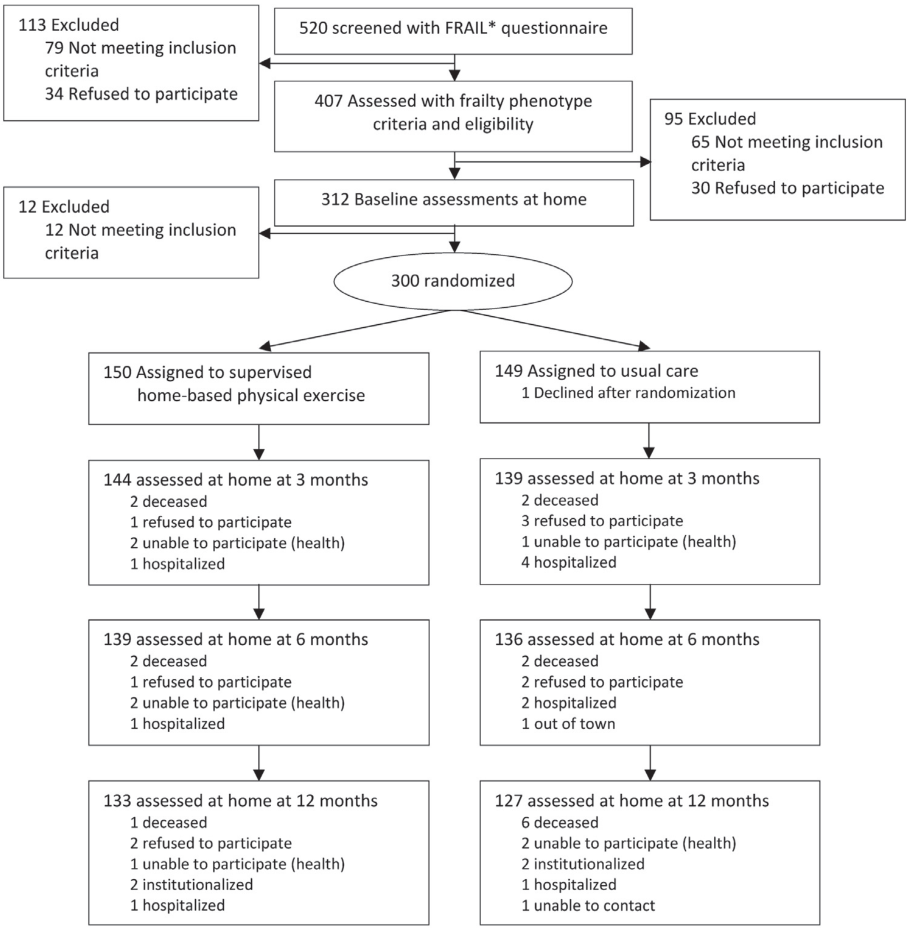
Our physical exercise intervention included brief counseling on physical activity as physiotherapists encouraged the participants to be active outside the supervised sessions. Even though the usual care group received no counseling, both groups increased their number of physical activity sessions per week in the first half of the trial. However, both groups decreased back to baseline level in the later half.

Training with the physiotherapists at home enabled people also in rural areas to participate in our study. Adherence to home-based programs has been better than in center-based programs[39] because older adults prefer activities close to home.[12] Furthermore, the effects of supervised home-based training on strength and functional ability have been greater,[40,41] and the intensity of the sessions can be higher[42] than in training without supervision. In our trial, supervision meant higher intervention expenses, but in the subgroup of frail participants, there was a decrease in total costs of social and health care services over 24 months compared with the frail participants in the usual care.[15]

As a strength, our study was a rigorously performed randomized controlled trial with good compliance. Furthermore, our sample was identified as frail or prefrail at baseline[43] based on 2 validated frailty assessments.[6,16] We also used validated measurements to assess functioning and physical performance, and the proportion of missing measurements during the intervention year was very low (13% at 12 months).

Study limitations

Falls and physical activity were self-reported, which is more unreliable than diaries[44] and objective measurements.[45] Our validated questions[25] included only frequencies of physical activities lasting



* FRAIL Fatigue, Resistance, Ambulation, Illnesses, Loss of weight

Fig 1 Flowchart of participants in randomized clinical trial. Numbers of participants.

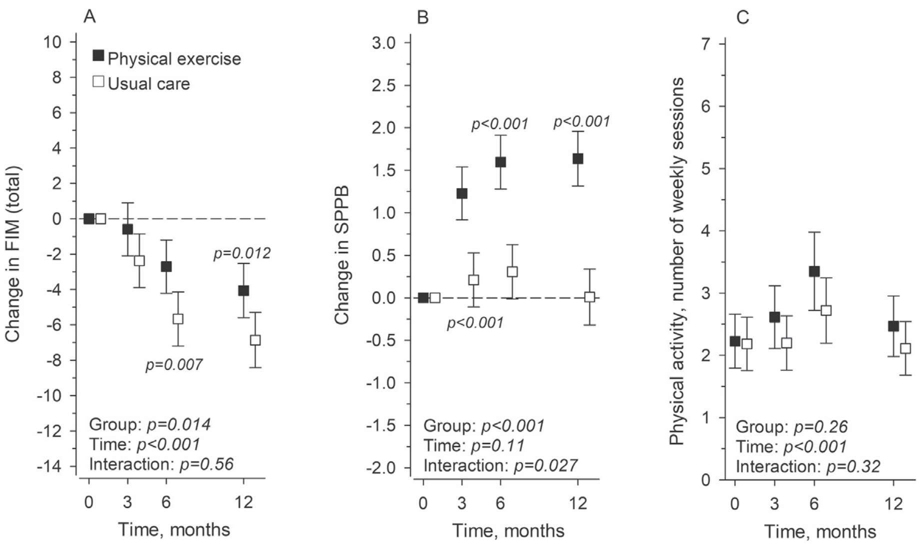


Fig 2 Mean changes in FIM (A) and in SPPB (B) and mean weekly frequency of physical activity sessions (C) in physical exercise and usual care groups over 12 months. Whiskers denote 95% CIs.

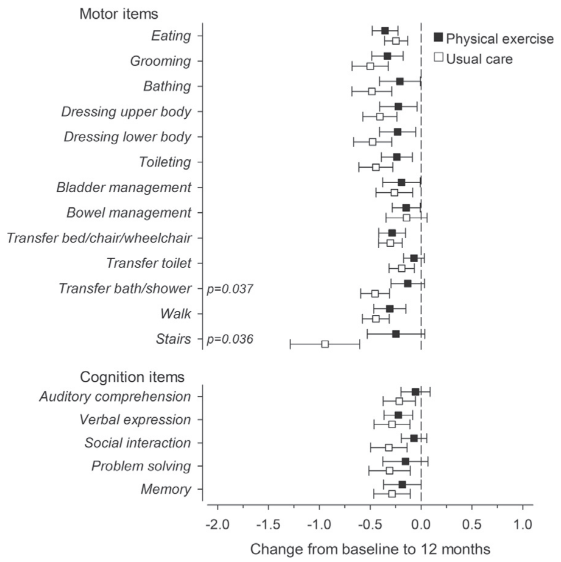


Fig 3 Mean changes in FIM items in the physical exercise and usual care groups from 0-12 mo. Whiskers denote 95% CIs. Benjamini-Hochberg step-up false discovery rate was applied to correct levels of significance for multiple testing in single FIM items.

>30 minutes but neither intensity nor exact duration. Therefore, our findings regarding falls and physical activity are only indicative and need to be interpreted with caution. In addition, the assessors were not blinded to the allocation status of the participants.

Conclusions

In conclusion, among people with signs of frailty, 12-month supervised, home-based exercise improved SPPB and decreased the number of falls. At 12 months, the physical exercise group had a better FIM than the usual care group, but there was no difference in IADL or handgrip strength between the groups. Supervised exercise did not enhance physical activity during leisure time.

Suppliers

a. Saehan, model Sh5001; Saehan.
b. Stata 16.1; StataCorp LP.

Keywords

Accidental falls; Aging; Frailty; Functional status; Physical functional performance; Physical therapy modalities; Rehabilitation

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Acknowledgments

We thank Kaija Paajanen, RN, and Virpi Äärimaa, LPN, for their valuable contribution to study recruitment and data collection. We thank the South Karelia Social and Health Care District's (Eksote) personnel for their contribution in recruiting participants.

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IV

CHANGES IN THE SEVERITY OF FRAILTY AMONG OLDER ADULTS AFTER 12 MONTHS OF SUPERVISED HOME-BASED PHYSICAL EXERCISE: A RANDOMIZED CLINICAL TRIAL

by

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Journal of the American Medical Directors Association 23(10): P1717.E9-1717.E15.

https://doi.org/10.1016/j.jamda.2022.07.010

ARTICLE IN PRESS

JAMDA xxx (2022) 1.e1–1.e7

JAMDA

journal homepage: www.jamda.com

Original Study

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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Keywords:
Frailty
older adults
physical exercise
rehabilitation

A B S T R A C T

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 5 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 the physiotherapist and included strength, balance, functional, and flexibility exercises twice a week at participants' homes.
Setting and Participants: Home-dwelling older adults aged ≥65 years who were frail (meeting 3-5 criteria) or prefrail (1-2 criteria) according to frailty phenotype criteria.
Methods: The severity of frailty (nonfrail, prefrail, or 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 prefrail 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 prefrail ($P = .032$) and frail ($P = .009$). At 12 months, the mean number of frailty criteria had decreased in the exercise group (−0.27, 95% CI −0.47, −0.08) and remained unchanged in the usual care group (0.01, 95% CI −0.16, 0.18; $P = .042$). The prevalence of the exhaustion ($P = .009$) and the low physical activity ($P < .001$) 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.

This work was supported by South Karelia Social and Health Care District (register number 1236/00.01.05.01/2013); the Social Insurance Institution of Finland (grant numbers 94/331/2013, 17/26/2019); and State Research Funding for Academic Health Research (Ministry of Social Affairs and Health, Finland), through Helsinki University Hospital (HUS) (grant numbers HUS 2016, HUS/2931/2017, HUS/2571/2017, HUS/2631/2019, and 864/2020).

The authors declare no conflicts of interest.
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https://doi.org/10.1016/j.jamda.2022.07.010
1525-8610/

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 aged ≥50 years, the prevalence is around 12%[10] and of people aged ≥80 years, 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 5 criteria: weight loss, exhaustion, low physical activity, slowness, and weakness.[18] A person is classified as frail if he or she fulfills 3 or more criteria and prefrail if they meet 1 or 2.[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 (eg, depression and 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 prefrailty or frailty, and on the prevalence of the 5 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 home care personnel. Preliminary eligibility was evaluated using the FRAIL questionnaire.[29,30] It contains 5 questions on Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, and has scores of 0 or 1, with the total score ranging from 0 to 5.[29,30] A potential participant who scored at least 1 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 1 of the physical frailty phenotype criteria,[18] a Mini-Mental State Examination[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 or drug abuse, severe problems with hearing or eyesight, a severe illness that is a contraindication for physical exercise (eg, cardiovascular, neurologic, or pulmonary disease) or a terminal disease (eg, cancer). All the eligible and willing participants signed their written informed consent.

Intervention

The participants in the exercise group participated in 1-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 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 8-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 (eg, physical and occupational therapy).

Outcomes

The severity of frailty was assessed using a slightly modified version of Fried's frailty phenotype criteria.[18] These 5 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, nonfrail; 1 or 2, prefrail; 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 >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 2 questions from the Center of Epidemiology Studies Depression scale[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 4 m 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 (eg, cane, rollator) were allowed. The person had 2 attempts, and the better result was used. The lowest fourth of the Short Physical Performance Battery[36] was used as the cutoff to enable validated and comparable times for both 4.0 and 2.44 m. The person met the modified slowness criteria if they walked slower than 0.46 m/s (walking time >8.7 seconds for 4 m and >5.2 seconds 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° angle next to the body, and the wrist in a neutral position. The best value of 3 attempts with the dominant hand was used. The cutoff 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), and ≤21 kg (BMI >29.0), and for men, ≤29 kg (BMI ≤24.0), ≤30 kg (BMI 24.1-28.0), and ≤32 kg (BMI >28.0). As background information, a Charlson Comorbidity Index[37] was calculated on the basis of medical record information, and alcohol consumption with Alcohol Use Disorders Identification Test–C questionnaire,[38] smoking habits and nutrition with Mini Nutritional Assessments[39] 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 SDs, or as frequencies with percentages. The relationship between the randomization groups and frailty status at baseline was evaluated using a 2-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 nonfrail, prefrail, 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. If the assumptions were violated, a bootstrap-type or permutation test was used. Hommel 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. Stata, version 17.0 (StataCorp LP), 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 1 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 65-98) years, 75% of the participants were women, and 184 participants were classified as prefrail and 115 as frail (Table 1).

Among those who were prefrail at baseline, in the exercise group, the status changed to nonfrail in 15 participants and frail in 7, and 5 died. In the usual care group, the status changed to nonfrail in 8 participants and frail in 20, and 7 died (Figure 2A). The transition frequencies from the prefrailty status were significantly different ($P = .032$) in the exercise and the usual care groups over 12 months.

Among the participants who were frail at baseline, in the exercise group 35 became prefrail and 3 nonfrail. In the usual care group, 17 became prefrail and 1 nonfrail, and 3 died. The transition frequencies from the frailty status over the 12 months were significantly different ($P = .009$) in the exercise and the usual care groups (Figure 2B).

The mean number of frailty criteria met at baseline was 2.2 (SD 1.1) in the exercise group and 2.2 (1.0) in the usual care group ($P = .82$) (Table 1). After 12 months, the change was −0.27, (95% CI −0.47, −0.08) in the exercise group and 0.01 (95% CI −0.16, 0.18) in the usual care group and the difference was significant ($P = .042$). As regards the single frailty criterion at baseline, the 3 most often met were exhaustion (62%), weakness (60%), and low physical activity (54%) (Table 1). After 12 months, one-third of the participants in the exercise group and half of those in the usual care group met the exhaustion criterion ($P = .009$) (Figure 3). The prevalence of the low physical activity criterion decreased to 14% in the exercise group, whereas it remained unchanged in the usual care group ($P < .001$). There were no differences between the groups in weight loss, slowness, or weakness criteria at 12 months, and no changes in the prevalence within groups (Figure 3).

The median number of completed exercise sessions was 96 (IQR 89, 99). The majority of participants reported mild and transient muscle soreness (58%) or mild joint pain (71%) after some exercise sessions. One fall led to mild injury. Eighteen participants took nitroglycerin during the session. On 5 occasions, the participants needed acute medical care (unrelated to exercise) at the arrival of the physiotherapist.

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 1 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 with the usual care group, more participants in the exercise group maintained their prefrail state or reversed to nonfrailty, 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 toward 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, 6 months of supervised, center-based physical exercise 5 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

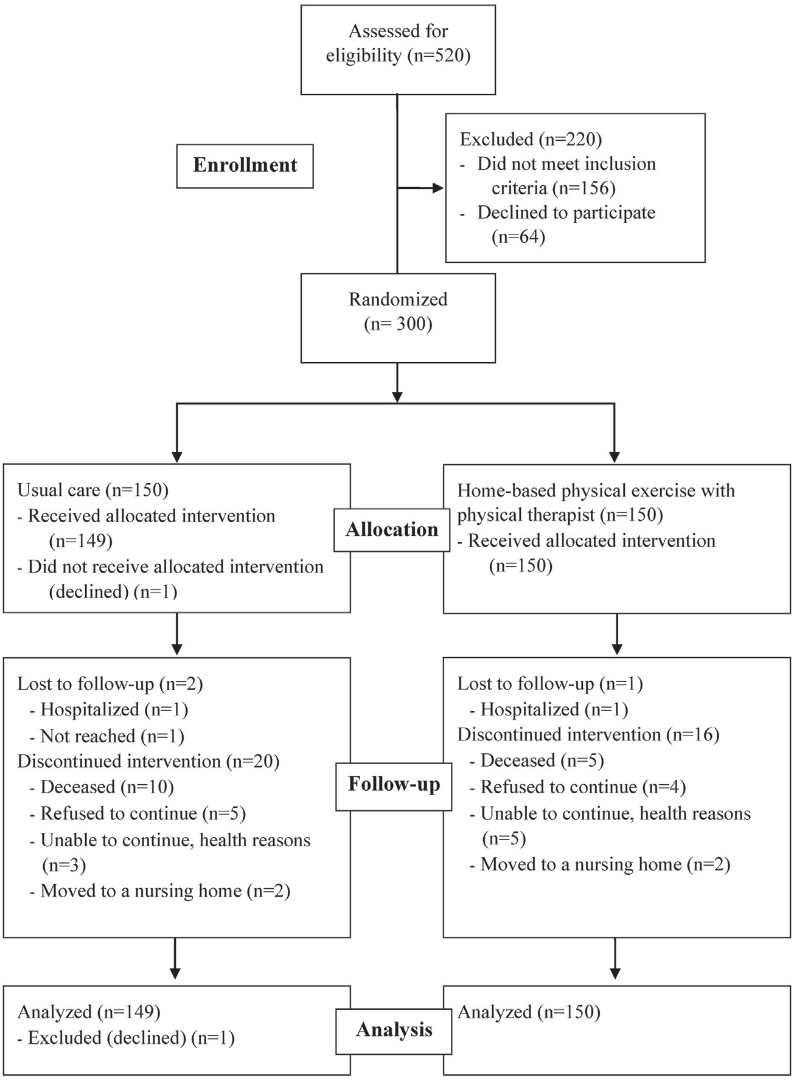

Fig. 1. Flowchart of study.

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, prefrail and frail people have fewer social networks than the nonfrail,[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 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 prefrail 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]

Table 1
Baseline Characteristics in Usual Care and Physical Exercise Groups, and in Subgroups of Prefrail and Frail

Characteristics	Usual Care: All (n = 149)	Physical Exercise: All (n = 150)	Usual Care		Physical Exercise		*P* Values[*]		
			Prefrail[†] (n = 92)	Frail[†] (n = 57)	Prefrail[†] (n = 92)	Frail[†] (n = 58)	Main Effects		Interaction
							Group	Frailty	
Women, n (%)	110 (74)	114 (76)	66 (72)	44 (77)	68 (74)	46 (79)	.68	.29	.98
Age, y, mean (SD)	83 (6)	82 (6)	82 (7)	84 (5)	82 (6)	82 (7)	.31	.32	.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)	.98	.46	.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)	.58	<.001	.84
Handgrip strength, kg, mean (SD)									
Women	17.8 (5.7)	17.1 (6.5)	18.6 (6.1)	16.6 (4.9)	18.7 (5.3)	14.8 (7.4)	.51	<.001	.90
Men	30.0 (7.5)	28.5 (7.5)	32.8 (6.6)	24.5 (6.3)	29.1 (8.4)	27.3 (5.3)	.82	.010	.028
Living alone, n (%)	86 (58)	88 (59)	43 (47)	43 (75)	54 (59)	34 (58)	.56	.013	.013
MMSE score, 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)	.32	.001	.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)	.67	.090	.41
Current smoking, n (%)	3 (2)	9 (6)	2 (2)	1 (2)	5 (5)	4 (7)	.094	.98	.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)	.51	.33	.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)	.069	<.001	.13
Frailty criteria, n (%)									
Weight loss	27 (18)	26 (17)	7 (8)	20 (35)	9 (10)	17 (29)	.98	<.001	.41
Low physical activity	83 (56)	77 (51)	30 (33)	53 (91)	32 (35)	45 (76)	.10	<.001	.075
Exhaustion	96 (64)	90 (60)	56 (62)	40 (69)	37 (41)	53 (90)	.28	<.001	<.001
Slowness	33 (22)	48 (32)	4 (4)	29 (50)	11 (12)	37 (63)	.020	<.001	.30
Weakness	85 (57)	94 (63)	37 (41)	48 (83)	49 (54)	45 (76)	.68	<.001	.25
Frailty score[‡], n (%)							.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)			

AUDIT-C, Alcohol Use Disorders Identification Test; CCI, Charlson Comorbidity Index; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment.
[*]A 2-way analysis of variance and logistic model including main effects of randomization groups and frailty status and their interaction.
[†]Participants were classified as prefrail if they met 1 or 2 of the frailty criteria and frail if they met 3 or more.
[‡]Number of frailty criteria fulfilled.

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 prefrail and frail people,[49] which enabled us to analyze the change in the severity of frailty as planned. Our participants had varied socioeconomic 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.

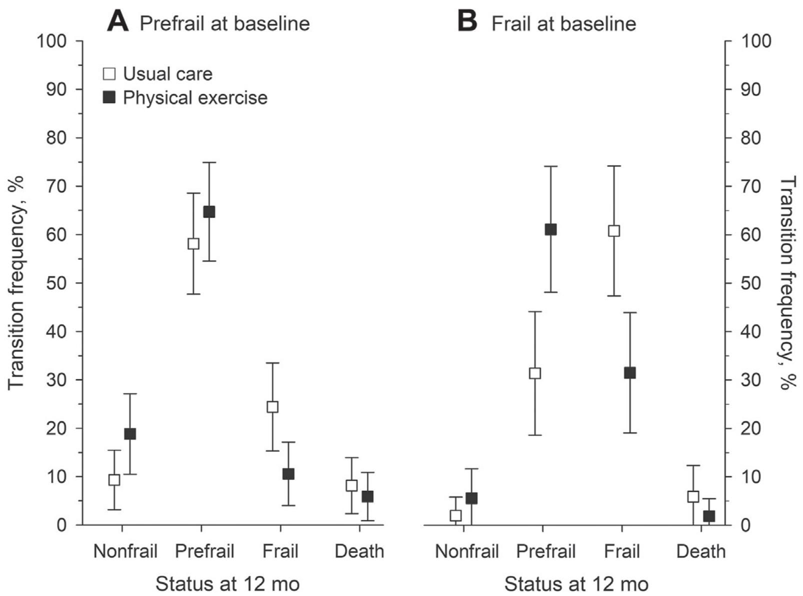

Fig. 2. (A) Status at 12 months for those who were prefrail at baseline by randomization groups (physical exercise and usual care). Transition frequencies (%) from prefrailty to the status of nonfrail, prefrail, frail, and death; mean with 95% CI whiskers. Statistical significance of transition frequencies between the randomization groups: $P = .032$. (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 nonfrail, prefrail, frail, and death; mean with 95% CI whiskers. Statistical significance of transition frequencies between the randomization groups: $P = .009$.

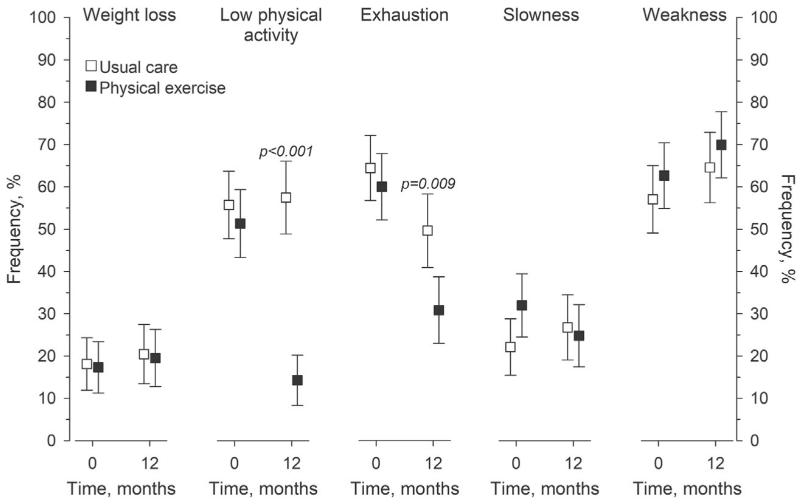

Fig. 3. Prevalence (frequency percentages, %) of the participants meeting the 5 frailty phenotype criteria (weight loss, low physical activity, exhaustion, weakness, and slowness) at baseline and at 12 months, by randomization groups (usual care and physical exercise); means with 95% CI whiskers. Hommel's multiple comparison procedure was used to correct significance; only statistically significant *P* values are presented.

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.

Acknowledgments

Kaija Paajanen, RN, and Virpi Äärimaa, LPN, for participant recruitment and data collection.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2022.07.010.

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