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PhD Thesis

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Cross-continuum rehabilitation following surgery for hip fracture - current knowledge and exploration of a new multimodal intervention.

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Table of contents

Abbreviations

ADL: Activities of daily living

RM: Repetition Maximum

VRS: Verbal Rating Scale

NMS: New Mobility Score

PSA: Prostate specific antigen

DEXA: Dual x-ray absorptiometry

BMD: Bone mineral density

LBM: Lean body mass

TUG: Timed Up and Go

DEMMI: The de Mortons Mobility Index

HRQoL: Health Related Quality of Life

GDS: Geriatric Depression Scale

FES-I: Falls Efficacy Scale International

MNA-SF: Mini Nutritional Assessment Short Form

BMI: Body Mass Index

AE: Adverse event

AR: Adverse reaction.

RCT: Randomized controlled trial

SMD: Standardized mean difference

CI: Confidence interval

GRADE: The Grading of Recommendations Assessment, Development and Evaluation

ROB2: Cochrane risk-of-bias tool, version 2

INT: Intervention group

CON: Control group

WHO: World Health Organization

PROM: Patient reported outcome measure

List of publications

The work of this thesis was carried out during my employment at the Department of Physiotherapy and Occupational Therapy at Hvidovre Hospital from 2018-2021.
The thesis includes 3 studies and 4 papers as listed below. The studies and papers will be referred to in the thesis as follows:

Study 1

Paper 1

Hulsbæk S, Juhl C, Røpke A, Bandholm T, Kristensen MT. Exercise therapy is effective at improving short- and long-term mobility, ADL and balance in older patients following hip fracture: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci.* Published online August 13, 2021.

Study 2

Paper 2

Hulsbæk S, Ban I, Aasvang TK, Jensen JEB, Kehlet H, Foss NB, Bandholm T, Kristensen MT. Preliminary effect and feasibility of physiotherapy with strength training and protein-rich nutritional supplement in combination with anabolic steroids in cross-continuum rehabilitation of patients with hip fracture: Protocol for a blinded randomized controlled pilot trial (HIP-SAP1 trial). *Trials.* 2019;20(1).

Paper 3

Hulsbæk S, Bandholm T, Ban I, Foss NB, Jensen JEB, Kehlet H, Kristensen MT. Feasibility and preliminary effect of anabolic steroids in addition to strength training and nutritional supplement in rehabilitation of patients with hip fracture: a randomized controlled pilot trial (HIP-SAP1 trial). *BMC Geriatr*. 2021;21(1):323.

Study 3

Paper 4

Hulsbæk S, Laursen LB, Kristensen MT, Midtgaard J. "It can't make things worse" – Older patients' perspectives on the use of anabolic steroids in rehabilitation following hip fracture: A Qualitative study embedded within a pilot RCT. (Under review in *Disability and Rehabilitation*, submitted 1. Sept. 2021)

Summary

Sustaining a hip fracture results in a vital loss of muscle strength, mobility and function. One year after the fracture around 50% of patients have not recovered their pre-fracture function. Consequently, the risk of subsequent falls, fractures and mortality is high. Existing evidence suggest that exercise has the potential to reduce loss of function after a hip fracture, yet more knowledge is needed to verify the effect of exercise therapy and explore the most effective exercise modality, intensity and timing of post-operative exercise therapy. Although exercise therapy might have the potential to reduce loss of function, it seems insufficient to fully overcome the negative impacts at short and long-term. Hence, a multimodal approach seems warranted to enhance recovery after hip fracture, and in that context, muscle enhancing medicine has been suggested. A recent Cochrane Review investigating the effect of anabolic steroids in rehabilitation following hip fracture was inconclusive, but recommended further research on effects, potential side effects and patients' attitudes toward such intervention.
The objectives of this PhD were to 1) evaluate the short- and long-term effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture and to explore if an effect was modified by trial level characteristics such as intervention modality, setting, duration and initiation timepoint; 2) investigate the feasibility and preliminary effect of a 12-week intervention adding anabolic steroid to physiotherapy and nutritional supplement in rehabilitation following hip fracture on knee extension strength and function; 3) to explore the patient perspectives of engaging in this multimodal intervention applying anabolic steroid in rehabilitation following hip fracture.

Study 1: The systematic review including 49 RCT studies involving 3904 participants showed a small to moderate effect of exercise therapy at short-term (end of intervention) on mobility (SMD 0.49, 95%CI 0.22-0.76); ADL (SMD 0.31, 95%CI 0.16-0.46); lower limb muscle strength (SMD 0.36, 95%CI 0.13-0.60); balance (SMD 0.34, 95%CI 0.14-0.54). At long-term (closest to 1 year) small to moderate effects were found for mobility (SMD 0.74, 95%CI 0.15-1.34); ADL (SMD 0.42, 95%CI 0.23-0.61); balance (SMD 0.50, 95%CI 0.07-0.94) and HRQoL (SMD 0.31, 95%CI 0.03-0.59). GRADE was used to evaluate certainty of the evidence and ranged from moderate to very low, due to study limitations and inconsistency. Subgroup analyses for short-term outcomes indicated that strength training improves strength, ADL-training improves ADL, and both functional training and strength training improves mobility and balance. Across the

outcomes large unexplained heterogeneity was present and therefore results should be interpreted with caution.

Study 2: In the pilot trial 717 patients were screened, and 23 randomized to either anabolic steroid or placebo in addition to physiotherapy (including strength training) and a nutritional supplement in a 12-week intervention. Target sample size of 48 participants was not reached, and the main limitations for inclusion were "not home-dwelling" (18%) and "cognitive dysfunction" (16%). Among the eligible patients, the main reason for declining participation was "Overwhelmed and stressed by situation" (37%). Adherence to anabolic steroid (87%) and exercise (91%) was excellent but poor for nutrition (61%). Addition of anabolic steroid showed a non-significant between-group difference on the primary outcome of knee-extension strength in the fractured leg of 0.11 (95%CI -0.25;0.48) Nm/kg in favor of the anabolic group. The corresponding %-change in knee-extension strength for the fractured leg from baseline to follow-up was median 178% (IQR, 41-263) for the intervention group and 50% (20-173) for the control group (p=0.28). For the non-fractured leg, a non-significant between-group difference of 0.16 (95%CI -0.05;0.36) Nm/Kg in favor of the intervention group was identified, and the %-change in knee-extension strength was median 31% (12-53) for the intervention group and 8% (0-33) for the control group (p=0.04). No significant between-group differences were identified for the secondary outcomes of physical performance, patient reported outcomes and body composition. 18 potential adverse reactions were identified but equally distributed between groups.

Study 3: Semi-structured telephone-based interviews of 19 participants were conducted at baseline and after the 12-week intervention. Qualitative content analysis revealed that the participants motivation for engagement in the trial was based on altruism and a trust that the intervention would 'do more good than harm'. They found randomization and possibility of receiving anabolic steroids intriguing. They especially valued trial participation because of their experience of getting extra care and 'deluxe' rehabilitation including close contact and support from the project coordinator and physiotherapist. The individualized progressive resistance training was perceived as challenging, but a key ingredient of their recovery.

In conclusion the systematic review showed low level of evidence for a small to moderate effect of exercise therapy on mobility, ADL, lower limb muscle strength and balance in older patients following hip fracture at short-term. At long-term low level of evidence was found for a small to moderate effect on mobility, ADL, balance and HRQoL. Results from the pilot RCT indicated that inclusion shortly after hip fracture surgery to a complex cross-continuum intervention seemed non-feasible due to slow recruitment. On the contrary adherence was high for both

injections and exercise, and no differences in adverse events between groups were identified. Although inconclusive regarding preliminary effect, positive tendencies were seen for the addition of anabolic steroid on knee-extension strength. The embedded qualitative study supported that the intervention was highly acceptable by the participants. The close contact and support from study staff and the individualized progressive strength training was perceived as motivating and might have promoted the participants feeling of self-efficacy.

Dansk resumé (Danish Summery)

Et hoftenært brud resulterer i et betragteligt tab af muskelstyrke, mobilitet og funktion. Selv et år efter bruddet har ca. 50% af patienter med et hoftenært brud ikke genvundet deres præ-fraktur funktionsniveau. Dette medvirker til en øget risiko for yderligere fald, frakturer og dødelighed. Den eksisterende viden indikerer, at træning kan reducere tab af funktion efter et hoftenært brud, men yderligere viden er nødvendig for at fastslå effekten af træning og betydningen af træningsmodalitet, intensitet og varighed. På trods af at træning formentlig kan reducere tab af funktion, så indikerer forskning, at træning alene ikke kan modvirke de store kort og langsigtede konsekvenser af et hoftenært brud. En multimodal tilgang kan være nødvendig for at optimere genvindelse af funktion og i den forbindelse er muskelopbyggende medicin er foreslået som en del af en sådan intervention. Et Cochrane review har undersøgt effekten af anabolsk steroid i rehabilitering af ældre med hoftenært bud, men forfatterne kunne ikke konkludere for eller imod, og anbefalede yderligere forskning for at afklare effekt, mulige bivirkninger og patienternes accept af en sådan behandling.
Formålene med denne afhandling var 1) at undersøge kort- og langtidseffekter af træningsterapi på fysisk funktion, selvstændighed og livskvalitet hos ældre patienter med et hoftenært brud, og om effekten kan være modificeret af studie-karakteristika som træningsmodalitet, varighed og træningssted; 2) at undersøge feasibility and præliminær effekt af en 12 ugers intervention bestående af anabolsk steroid i tillæg til fysioterapi og ernærings tilskud i genoptræning efter et hoftenært brud målt på knæekstensionsstyrke og funktion; 3) at undersøge patienternes perspektiv på en sådan multimodal intervention indeholdende anabolsk steroid.

Studie 1: Den systematiske litteraturgennemgang resulterede i 49 RCT-undersøgelser med 3904 deltagere og viste en lille til moderat effekt af træningsterapi på kort sigt (afslutning af intervention) på mobilitet (SMD 0,49, 95%CI 0,22-0,76); ADL (SMD 0,31, 95%CI 0,16-0,46); muskelstyrke i under ekstremiteterne (SMD 0,36, 95%CI 0,13-0,60) og balance (SMD 0,34, 95%CI 0,14-0,54). På lang sigt (tættest på 1 år) blev der fundet små til moderate effekter for mobilitet (SMD 0,74, 95%CI 0,15-1,34); ADL (SMD 0,42, 95%CI 0,23-0,61); balance (SMD 0,50, 95%CI 0,07-0,94) og HRQoL (SMD 0,31, 95%CI 0,03-0,59). GRADE-metoden blev brugt til at evaluere den samlede kvalitet af evidensen for hvert effektmål og varierede fra moderat til meget lav på grund af studie-begrænsninger og inkonsistens. Subgruppeanalyser indikerede at styrketræning forbedrer styrke, ADL-træning forbedrer ADL og både funktionel træning og

styrketræning forbedrer mobilitet og balance. Pga. af stor uforklarlig heterogenitet på tværs af effektmålene bør resultaterne tolkes med forsigtighed.
Studie 2: I det randomiserede kontrollerede pilot-studie blev 717 patienter screenet og 23 randomiseret til enten anabolsk steroid eller placebo i tillæg til fysioterapi (med styrketræning) og et proteinrigt ernæringstilskud i en 12-ugers intervention. Den forudbestemte stikprøve-størrelse på 48 patienter blev ikke nået. De største begrænsninger for inklusion var "ikke hjemmeboende" (18%) og "kognitiv dysfunktion" (16%). Blandt de mulige patienter for inklusion var hovedårsagen til at takke nej "Overvældet og stresset af situationen" (37%). Compliance var høj for både anabolske steroider (87%) og træningsintervention (91%), men mindre for ernæring (61%). Supplementet med anabolsk steroid resulterede i en ikke-signifikant forskel mellem grupperne i knæekstensionsstyrke på fraktur benet på 0,11 (95%CI -0,25; 0,48) Nm/kg til fordel for interventionsgruppen. Den tilsvarende procentuelle ændring i knæ-ekstensionsstyrke for fraktur benet fra baseline til opfølgning var median 178% (41-263) for interventionsgruppen og 50% (20-173) for kontrolgruppen (p=0,28). For det ikke-frakturerede ben sås en ikke-signifikant forskel mellem grupperne på 0,16 (95 %CI -0,05; 0,36) Nm/Kg til fordel for interventionsgruppen, og her var den procentuelle ændring i knæekstensionsstyrke median 31% (12-53) for interventionsgruppen og 8% (0-33) for kontrolgruppen (p=0,04). Der blev ikke identificeret signifikante forskelle mellem grupper for de sekundære effektmål. 18 potentielle uønskede reaktioner blev identificeret, men de var ligeligt fordelt mellem grupper.
Studie 3: Semistrukturerede telefoninterviews med 19 deltagere blev udført ved baseline og efter interventionen. Kvalitativ indholdsanalyse viste at deltagernes motivation for at indgå i studiet var baseret på altruisme og en tillid til, at interventionen ville 'gøre mere gavn end skade'. De fandt randomisering og muligheden for at modtage anabolske steroider spændende. De værdsatte især deltagelse i studiet på grund af hvad de opfattede som ekstra omsorg og ’luksus’ genoptræning og fremhævede den tætte kontakt og støtte fra projektkoordinatoren og fysioterapeuterne. Den progressive styrketræning blev opfattet som udfordrende af deltagerne, men også som en afgørende ingrediens i deres genvindelse af funktionsevne.

Opsummerende viste resultaterne af denne afhandling lav evidens for en lille til moderat effekt af træningsterapi til ældre patienter efter et hoftenært brud på mobilitet, ADL, muskelstyrke i underekstremisterne og balance på kort sigt. Tilsvarende blev der fundet lav evidens for en lille til moderat langsigtet effekt på mobilitet, ADL, balance og livskvalitet. Derudover viste resultaterne fra pilotstudiet, at det var svært at inkluderer patienter de første dage efter operationen for et hoftebrud til en kompleks tværsektoriel intervention. Dog var compliance høj

for både anabolsk steroid og træningsinterventionen, og der blev ikke vist forskelle i bivirkninger mellem grupperne. Selvom præliminær effekt ikke kan fastslås, sås positive tendenser for virkningen af anabolsk steroid på knæekstensionsstyrke. Den integrerede kvalitative undersøgelse viste stor accept af interventionen fra deltagernes side. Især den tætte kontakt og støtte fra det involverede sundhedspersonale og den progressive styrketræning var værdsat og blev opfattet som motiverende, hvilket kan have medvirket til at fremme ”self-efficacy” blandt deltagerne.

Introduction

Hip Fractures – Epidemiology (incidence and consequence)

Worldwide, there are large geographical variance in the incidence of hip fractures, with the absolute highest rates in Scandinavia and the lowest rates in developing countries such as Africa and Latin America.[1,2] In 2012 Denmark took a non-favorable 1st place among 63 countries with the highest age standardized annual incidence among women (574/100,000) and men (290/100,000).[1] In Denmark approximately 6500 persons aged 65 years or older are operated for a hip fracture every year.[3] The average age is 83 years and the proportion of women is around 70%.[3] The incidence has been decreasing over the last decade, probably due to effective prevention strategies and a general healthier ageing. However, it is anticipated that the demographic changes with an increase in the proportion of elderly, will result in an increase or at least maintain incidence rates.[4,5] Internationally, tendencies in high income countries are comparable to Denmark, where the incidence has leveled off or decreased, whereas for low and middle income countries the incidence rates are still increasing.[1,2]

Hip fractures constitutes a major challenge for the individual, healthcare systems and society. People recovering from a hip fracture experience loss of muscle strength in the fractured leg of approximately 50% compared to the non-fractured leg within the first weeks after surgery.[6–8] This loss of strength persists with around 17-31% two to three months after the facture[9,10] and 12-38% six to nine months after the fracture.[10–12] Concurrently, mobility and function are severely reduced at both short and long-term,[13–15] and at one year after the fracture around 50% still have not regained pre-fracture function.[13,16,17] This reflects on the patient's independence and self-care, which results in increased need for homecare or even change of residence,[13] and additionally many patients experience loss of health-related quality of life.[13,18,19] As physical function deteriorates the risk of falls and subsequent fractures increases.[20–22] Mortality rates after hip fracture are high, and in Denmark 30-day mortality is around 10% and 1-year mortality approximately 28%.[3] In addition, older adults sustaining a hip fracture have a 5- to 8- fold increased risk for all-cause mortality within the first 3 months after the fracture,[23] and an excess mortality at least the double of aged matched populations at both short and long-term.[23–25] Thus, hip fractures constitutes a substantial economic burden to the health care systems and society in general, and costs are expected to increase according to the aging population.[26–28] A Danish study has evaluated the costs related to osteoporotic fractures, and they reported hip fractures to

be the absolute most expensive osteoporotic fracture type, with the municipalities holding the majority of the costs related to e.g. care delivery and rehabilitation.[28]

Classification, perioperative challenges and treatment

Hip fractures are situated in the proximal femur and classified according to location: 1) Intracapsular fractures, which are fractures of the femoral neck, they occur within the hip capsule and are further classified according to displacement. 2) Extracapsular fractures occur in the trochanteric area and are divided in intertrochanteric fractures and subtrochanteric fractures, and may be subdivided based on displacement and degree of fracture comminution.[29] Extra capsular fractures are associated with more pain and edema and reduced quadriceps strength, function and higher mortality,[30–33] thus fracture type is a relevant factor to consider in rehabilitation. In Denmark the distribution of fracture type is 55% intra capsular fractures and 45% extracapsular fractures.[3] The surgical treatment is performed according to an algorithm including factors such as fracture type, displacement and age.[34]

As a consequence of trauma and surgery patients are exposed to a stress response of endocrine-metabolic changes and inflammatory reactions, which causes hypermetabolism and catabolism, immune suppression and organ dysfunction.[35] This potentially causes complications in the form of infections, slow wound healing, muscle wasting, cardiac/thromboembolic complications, nausea, ileus, pain, fatigue and cognitive dysfunction.[35,36] The perioperative treatment of hip fractures at Hvidovre Hospital are based on principles of fast-track surgery[35] aiming at reducing the complications caused by surgical stress. Among others, the treatment protocol includes epidural anesthesia until the fourth post-operative day, a standardized liberal transfusion protocol (transfusion if hemoglobin (Hb) is < 9.7 g/dl.), d-vitamin and calcium supplementation, fluid and nutrition management and early mobilization (within the first 24 hours of surgery).

Despite the enhanced recovery program patients with hip fracture still faces an immediate (1st week of surgery) loss of knee extension strength in the fractured leg.[6–8] The immediately post-operative loss of muscle strength is multifactorial and not completely understood, but it is presumably a consequence of two factors: 1) Trauma and surgery leading to a failure of the central nervous system to activate muscles close to the operated joint caused by tissue damage, edema, inflammation and pain, and is referred to as arthrogenic muscle inhibition.[37–39]
2) Immobilization and muscle disuse affecting the neuromuscular system leading to an atrophy response within few days.[40,41]

Elderly patients and predisposing factors for a hip fracture

Osteoporosis and falls

Two main modifiable disposing factors for hip fractures in older patients are osteoporosis and falls. Osteoporosis is characterized by reduced bone mass and microarchitectural deterioration of the bone tissue, resulting in bone fragility which makes it prone to fractures with even a small impact or stress.[26] Bone mineral density (BMD) is used to determine if an individual has osteoporosis, and the diagnostic criteria, developed by WHO is BMD 2.5 SD or more below the young female adult mean.[26,42] A clinical diagnosis can be made on the presence of a fragility fracture, as the first presentation of osteoporosis often is a fracture. The risk of osteoporosis increase with age and osteoporosis is more prevalent in women compered to men.[26]

Most hip fractures in people 65 years and older occur as a result of a fall from standing height and are referred to as 'low energy' fractures or fragility fractures.[43] Many factors can facilitate the occurrence of falls among older people. These factors although interrelated are often divided into two major groups: 1) Intrinsic risk factors inherent to the person and related to the biological and psychosocial changes associated with aging e.g. advanced age, history of previous falls, muscle weakness, gait and balance problems, poor vision, and chronic diseases. 2) extrinsic risk factors, which results from the interaction of the elderly with the environment e.g. medication use or environmental hazard as slippery/uneven surfaces, poor lighting and poor access to public areas.[44,45] Falls can, besides leading to a fracture, have a psychological consequences in the form of 'fear of falling' and anxiety, which can result in self-restricted activity and further contribute to deconditioning, weakness and additional risk of further falls.[46] Figure 1 depicts how falls and fall related injuries such as a hip fracture, can result in a downward spiral of deconditioning.

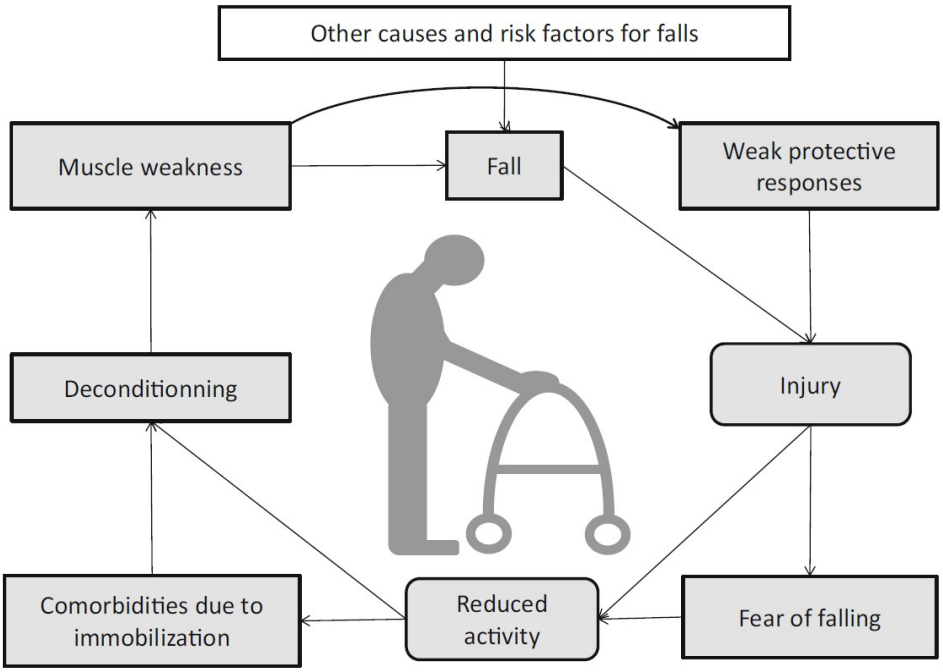

Figure 1: Downward spiral as a consequense of falls and related injuries.
Reprinted with permision from Springer Nature: Benichou 2016 [47]

Sarcopenia

Sarcopenia is a major risk factor for falls and fractures and is associated with negative health outcomes such as loss of mobility and independence, reduced quality of life, cardiac/respiratory disease, cognitive impairment and death.[48–50]

Sarcopenia has been defined as a progressive and generalized skeletal muscle disorder that involves accelerated loss of muscle function.[48] It was recognized by WHO as an independent condition in 2016.[48] The definition of sarcopenia has evolved over the years, and still international consensus is lacking on definition and cut off points.[48–50] A widely recognized and recently updated operational definition of sarcopenia is from The European Working Group on Sarcopenia in older people (EWGSOP).[49] They define sarcopenia by 3 criterions: 1) Low muscle strength (probable sarcopenia is identified). 2) Low muscle quantity or quality (confirms diagnosis). 3) Low physical performance (determines severity).[49] This updated definition uses low muscle strength as the principal determinant of sarcopenia, as muscle strength is superior to muscle mass in predicting adverse outcomes, and it is a more accessible measure in the clinic.[49] The loss of muscle strength, mass and function is a multifactorial process. Some of the contributors are age, malnutrition/malabsorption, inactivity, diseases (inflammatory, neurological, trauma etc.).[48,49] Sarcopenia typically progress gradually, but it can be acutely accelerated by immobilization and stress inducing events (illness, trauma, surgery).[43]

Aging leads to multiple changes in the neuromuscular system, and the loss of skeletal muscle mass can mainly be attributed to type II fiber atrophy and fiber loss.[43,51] Type II fibers are critical for rapid muscle force production during contraction, therefore type II fiber atrophy may predispose to falls.[43,47]

The prevalence of sarcopenia in patients with hip fracture has been estimated to be between 17-74% depending on definition of sarcopenia and population.[52–56] Sarcopenia in patients with hip fracture is associated with worse outcomes and higher mortality than in non-sarcopenic patients with hip fracture.[43,55,57,58] Landi and colleagues showed, that sarcopenic hip fracture patients had a significant worse overall function evaluated by Barthel Index both at time of discharge from the rehabilitation unit and after 3-months.[57] Corresponding, Kristensen et al. found that patients probable sarcopenic performed worse in mobility, had lower pre-fracture function and expressed a greater fear of falling than their stronger counterparts.[55]

The suggested management of sarcopenia is resistance training and a protein-rich diet.[48,59] D-vitamin supplementation and muscle enhancing medicine have been suggested, but evidence of the effect is still limited.[48,59,60] As such, sarcopenia is prevalent in patients with hip fracture and shares largely the same consequences and management recommendations. Therefore, multicomponent interventions seem of pivotal importance to reduce the risk of decline in function and other related consequences among patients with hip fracture.

Exercise therapy after hip fracture

The World Health Organization (WHO) defines rehabilitation as "a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment."[61] The Danish definition of rehabilitation from the Danish Rehabilitation Forum and Marselisborg Centre is slightly more detailed: "A goal-oriented, cooperative process involving a member of the public, his/her relatives, and professionals over a certain period of time. The aim of this process is to ensure that the person in question, who has, or is at risk of having, seriously diminished physical, mental and social functions, can achieve independence and a meaningful life. Rehabilitation takes account of the person's situation as a whole and the decisions he or she must make, and comprises co-ordinated, coherent, and knowledge based measures."[62,63] This thesis mainly focuses on the physical part of rehabilitation and exercise therapy. The term rehabilitation when used in this thesis reflects this.

Exercise therapy is an important part of treatment and rehabilitation in patients with hip fracture. In Denmark there is no national clinical guideline for rehabilitation following hip fracture, albeit

an older reference program from 2008 exists with recommendations on treatment, care and rehabilitation.[64] Nonetheless, rehabilitation is typically divided in acute hospital rehabilitation and municipality-based rehabilitation, and the overall aim is to reduce disability and to regain previous level of function. Acute-hospital rehabilitation is initiated on the first post-operative day with focus on early mobilization and exercises aiming at improving basic ambulatory skills to a level that allows patients to be discharged to their previous place of residence. Both physiotherapy and occupational therapy could be provided, but there are regional differences. According to the Danish national registry for hip fractures 95% of patients are referred to municipality based physical rehabilitation following discharge.[3] However, there are large variations in the municipality based physical rehabilitation with around 50% of municipalities not having a formal description or a specific program for intervention offered to patients with hip fracture.[65] As such content, intensity and the length of the intervention could vary considerably.

Previous research has sought to establish the effect of exercise therapy and physical rehabilitation following hip fracture. Two Cochrane reviews evaluating the effect of mobilization strategies and rehabilitation interventions after hip fracture were inconclusive, but they indicated a possibility to increase mobility and independence after hip fracture, although the optimal method remained unclear.[66,67] Additionally, a review by Diong et al. showed a small significant effect of structured exercise on mobility,[68] but on the contrary Beckmann et al. found no statistical significance of exercise therapy for either outcomes of mobility, balance, walking speed or endurance within the first three months after surgery.[69] Several smaller systematic reviews and meta-analysis have investigated the effect of specific exercise modalities, particularly indicating positive effects of progressive strength training and balance training,[68,70–73] and others have tried to establish the effect of exercise characteristics such as setting and timing.[74,75] Generally, the studies indicated positive effects, but they were limited by few trials and large heterogeneity. As such, more evidence is needed to establish the effect of exercise therapy and the most effective exercise modality, intensity and timing of post-operative hip fracture rehabilitation. Additionally, a larger amount of new trials have been published within the last years, which requires an update on the effects of exercise therapy in older patients following hip fracture.

Muscle enhancing medicine and nutrition

Although existing evidence suggest that exercise therapy might be able to reduce the negative consequences of a hip fracture, exercise as a single intervention still seems insufficient to fully overcome the major short and long-term negative impacts. Consequently, suggestions for future research is to focus on multimodal interventions, that might include pharmacology and nutrition.[13–15,51] In figure 2, a theoretical model of physical capacity over time is illustrated with the assumed different trajectories of recovery after a hip fracture.

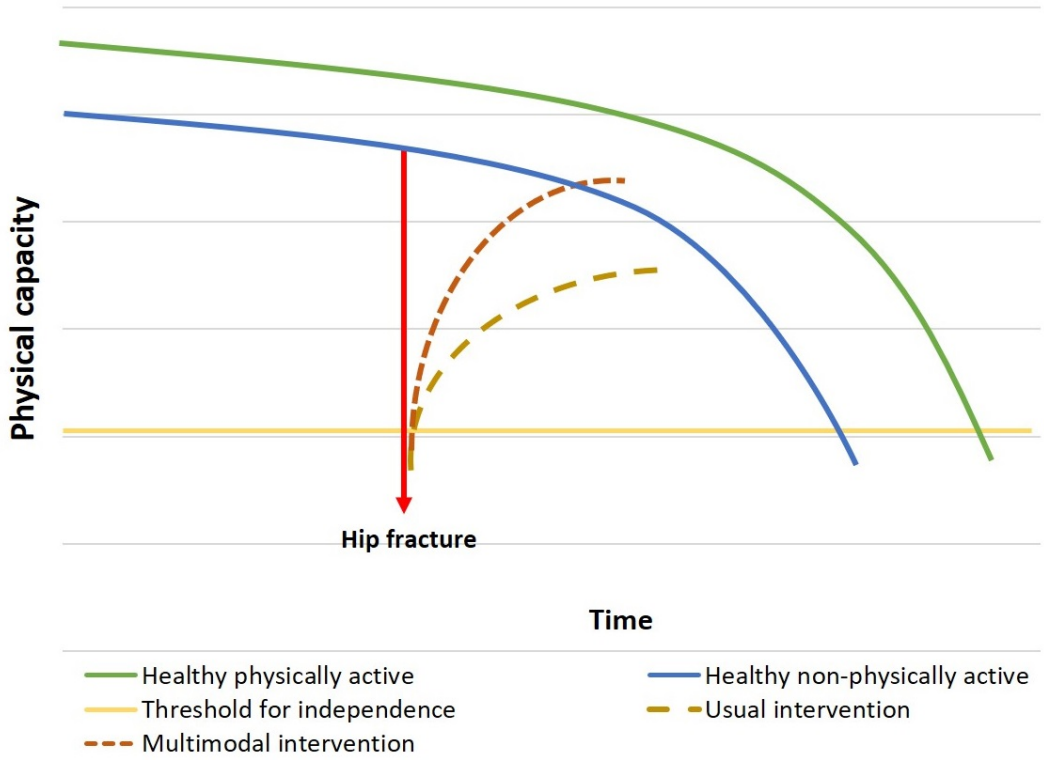

Figure 2: A theoretic model of the age-related decline in physical capacity over time. Healthy physically active people have a higher level of physical capacity compared to the non-active, and they reach the threshold for not being independent in everyday activities at a later age. When a hip fracture occurs a sudden loss of function occurs and physical capacity declines to a level of dependency in basic mobility and activity (e.g. rise from a chair, walking, toileting). Patients partially recovery function with usual intervention but are likely to have a larger recovery from a multimodal intervention. *(Inspired by Magaziner 2015[15] and Suetta 2007[76])*

Muscle enhancing medicine has been suggested as an addition to exercise to further enhance recovery after hip fracture, as it may slow down the accelerated loss of muscle mass and strength after hip fracture.[14,47,77,78] Pharmacologic preparations suggested is sex steroids, growth hormone, selective androgen receptor modulators (SARMs) and myostatin inhibitors.[14,47] In this

PhD the focus is on synthetic anabolic-androgenic steroid (nandrolone decanoate) which has the properties of being protein-building, promoting mineralization of the bones and stimulating the formation of red blood cells.[79] Nandrolone is structurally related to the natural occurring testosterone, but it provides an enhanced anabolic effect and a reduced androgenic effect,[79] which is an important factor, as it is provided for both genders.
A systematic Cochrane review has investigated the effect of anabolic steroids in rehabilitation following hip fracture, and although inconclusive, positive tendencies were seen in relation to activities of daily living (ADL), gait speed, and reduction in loss of muscle mass.[78] Likewise, in other population facing similar challenges in regard to decrease in muscle strength and function e.g. elderly with chronic obstructive pulmonary disease, osteoporosis and patients in hemodialysis positive effects were seen on Quality of Life (QoL), Lean body mass (LBM), BMD, hemoglobin levels, strength and function.[80–83] As such the existing literature suggest that further high-quality trials of the effect of anabolic steroids in elderly with hip fracture are warranted.[14,51,77,78]

Malnutrition and low protein intake, in older hospitalized patients, is common and is considered a challenge towards optimal recovery after hip fracture.[43,51,84] Particular, as adequate protein intake may prevent muscle wasting and be beneficial in reducing the functional decline.[43]
Further, it seems reasonable, in order to benefit optimally from exercise interventions and muscle enhancing medicine, that necessary nutrients should be available to accrue muscle mass.[47]
However, the effectiveness of oral nutritional supplements in patients with hip fracture are not persuasive. A systematic Cochrane review of the effect of nutritional supplementation for older patients recovering from hip fracture conclude, that there might be some effect in relation to reducing complications within the first 12 month, but the evidence is weak.[84] Additionally, a recent narrative review concludes that nutritional supplements may decrease complications and shorten length of stay, but until now the effectiveness of nutritional supplements on functional recovery, discharge destination and mortality is still uncertain.[43]

Based on this knowledge and existing evidence it seems reasonable and highly demanded to evaluate the effect of a multimodal intervention adding muscle building medicine to exercise therapy and nutritional supplement to enhance short- and long-term outcomes after a hip fracture. Considering the complex nature of such multimodal intervention it seems relevant to further qualify the trial by exploring the patients experiences and acceptability of engaging in the trial to gain further insight in the various complex social and behavioral processes.[85,86] The

patient perspective of the use of anabolic steroid in rehabilitation is of high relevance, as anabolic steroids are often associated with abuse in athletes and fitness environments, rather than the medical advantages of the drug, and as such it might cause scepticism towards engaging in a trial using anabolic steroids. Furthermore, it is well established that recruitment efficacy declines with increasing age of participants and especially recruitment of acute hospitalized geriatric patients is known to be challenging.[87,88] Thus, the patient perspective and their motivation to engage in a multimodal complex intervention including anabolic steroids is relevant to inform findings of the pilot trial, but also in relation to planning future trials and treatment of patients with hip fracture.[89]

Objective

The overall aim of this PhD thesis was to investigate the effect of exercise therapy in rehabilitation of older patients after hip fracture and to explore a novel multimodal intervention adding muscle enhancing medicine to the rehabilitation phase for older patients following hip fracture surgery.

Study 1

The aim of the systematic review was to evaluate the short- and long-term effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture initiated from the time of surgery until 1 year after surgery, and secondly, to determine if the effect of exercise therapy was modified by trial level characteristics such as intervention modality, setting, duration and initiation timepoint.

Research questions

1. What is the effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture, when the intervention is initiated within the 1st year after surgery?
2. Is the effect of exercise therapy modified by the following trial level characteristics: Initiation point of intervention, setting, duration of intervention, intervention modality, comparator being active/passive, comprehensiveness of interventions, and risk of bias?

Study 2

The aim was to investigate the feasibility and preliminary effect of a 12-week intervention consisting of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement on knee extension strength and function at 14-weeks follow-up after hip fracture surgery.

Hypothesis

1. An intervention consisting of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement, is a feasible and preliminary safe treatment in elderly patients with hip fracture when initiated in the acute orthopaedic ward and continued for 12 weeks.
2. That anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement is preliminary more efficacious in improving muscle strength and physical function 14 weeks after hip fracture surgery compared to placebo, physiotherapy and protein-rich nutritional supplement.

Study 3

The aim was to explore patient perspectives on a multimodal intervention consisting of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement following hip fracture.

Research questions

1. What motivates elderly with hip fracture to engage in a clinical trial involving anabolic steroids in rehabilitation?
2. How does elderly with hip fracture evaluate participation in a randomized clinical trial using anabolic steroids in rehabilitation?

Methods

In the below section an overview of the research methods applied in the thesis are provided. As three different methodological approaches have been used, the method of each study is described separately. For detailed descriptions, please see the full papers 1-4 in the appendix.

Study 1

The following section is based on paper 1.[90]

Design and eligibility criteria

Study 1 is a systematic review and meta-analysis of randomized controlled trials (individual and cluster) and quasi-randomized controlled trials investigating the effect of exercise therapy interventions on several outcomes of physical function and wellbeing. The study was pre-registered with the international prospective register of systematic reviews (PROSPERO) in February 2020 (CRD42020161131). Eligibility criteria are illustrated in table 1. Bibliographic databases were searched up to 16th November 2020: Medline (PubMed), Cochrane Central register of Controlled Trials (CENTRAL), Embase (Ovid), CINAHL (EBSCO) and PEDro.

Study selection and data collection

Titles and abstracts were independently screened by three reviewers, and duplicates were removed. Discrepancies between reviewers were discussed until consensus was reached. Two reviewers independently conducted full text screening.

Trial level characteristics was extracted by one reviewer and confirmed by a second reviewer. Two reviewers independently retrieved effect sizes. If an outcome was assessed at several follow-up timepoints, the timepoints synthesized was short-term (end of intervention) and long-term (closest to 1 year). The following data was extracted: Author, year of publication, country, number of participants, age, gender, study period, primary intervention modality, description of intervention, primary setting, initiation timepoint following surgery, duration of intervention, providers of intervention, supervision, characteristic of comparator, outcomes, follow-up timepoint, adherence, adverse events and trial registration.

Table 1: Eligibility criteria

Population	Patients operated for a hip fracture. Mean age of study population ≥ 60 years.
Intervention	Exercise therapy is defined as exercise interventions, that were or could be led by physiotherapists or occupational therapists. The intervention should include interaction between physiotherapists/occupational therapists and the patient; thus, a written instruction was not considered exercise therapy. Multidisciplinary interventions including medical or nursing interventions were not included.
Comparator	Usual care, a different intervention, or no intervention
Outcome	Prioritized list of outcome domains: 1) Mobility Composite mobility measures (scales seeking to measure different aspects of mobility) had the highest priority, and hereafter measures of walking ability (e.g. gait speed). Objective measures ranked higher than self-reported measures. 2) Activities of daily living (ADL) Objective measures of ADL ranked higher than self-reported measures. 3)Health Related Quality of Life (HRQoL). If a total score was not provided, the most general subscore was used. 4)Muscle strength in the lower limb Direct measures (e.g. specific muscle strength test) before surrogate measures (e.g. Chair Stand Test). If several measures of 'direct' lower limp muscle strength were reported, priority was as follows: Knee-extension, leg-press, hip abduction, hip extension, calf (plantar flexion), knee flexion. The prioritization was based on anti-gravity muscles first. If knee-extension was measured on both affected and unaffected side, affected side were prioritized. 5)Balance Direct (e.g. balance platform) before indirect, and composite measures of balance before a single measure. 6)Endurance Direct measures (e.g. VO2max) before indirect (e.g. 6 min walk). 7)Physical activity Upright time, time walking, sedentary time were prioritized first. Secondly, number of steps and lastly self-reported measures. 8)Fear of falling 9)Falls (only if specified as outcome)
Time frame	Interventions initiated within the first year after surgery.
Note: Papers in English, Danish, Swedish, Norwegian and German were eligible publication after 1990, due to expected change in rehabilitation.	

Content in the table based on Hulsbæk 2021[90]

Quality assessment

Risk of bias for the effect estimates in the individual studies were assessed using Cochrane Risk of Bias Tool 2 (ROB2).[91] Assessment of certainty of the body of evidence was conducted using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE).[92]

Summery measures and data synthesis

Number of participants, change score and corresponding standard deviation (SD) were extracted for intervention group and control group as suggested by the Cochrane Handbook.[93]

The random effects model (restricted maximum likelihood method, REML) was used to pool the effect of the individual studies, as heterogeneity was expected because of differences in participants, interventions and outcome. The pooled effect size was expressed as a standardized mean difference (SMD) and calculated by dividing the mean group difference with the pooled standard deviation (SD). Heterogeneity was examined as between study variance (tau2) and as I^2-statistics measuring the percentage of variation attributable to inconsistency. The level of significance was set at $p<0.05$.

The influence of the following trial level characteristics was investigated in subgroup analyses: Initiation of intervention, Primary setting, Duration of intervention, Intervention modality, Control intervention, Comprehensiveness of intervention and Risk of bias. Test for subgroup difference was conducted, and a p-value of less than 0.1 indicated a statistically significant subgroup effect.[94] The analyses were performed using STATA version 16.

Study 2

The following section is based on paper 2[95] and paper 3.[96]

Design and population

Study 2 is a randomized, blinded, single-center, placebo-controlled, two-armed, parallel-group, superiority pilot trial. The trial was approved by the Capital Region's Research Ethics Committee (H-18004495) and the Danish Medicine Agency (EudraCT: 2017-001543-13) and registered with the Danish Data Protection Agency, Journal no.: AHH-2017-090, I-Suite No.: 05980. It adhered to the principles of ICH-GCP and was monitored by a Good Clinical Practice (GCP) Unit. Pre-registration at ClinicalTrials.gov, registration number NCT03545347 (04/06/2018).

Patients admitted to the Hip Fracture Unit, at the Department of Orthopaedic Surgery, Copenhagen University Hospital – Hvidovre, were screened for eligibility from June 2018 to February 2020. Eligibility criteria are shown in Table 2. Patients complying to the criteria were addressed at the ward 1-4 days post-surgery, where full oral and written information was provided by the PhD student. The patients were hereafter offered a minimum of 24 hours to

consider participation and were provided the opportunity to have a next of kin accompanying for further information. Informed consent was signed by patients who agreed to participate.

Table 2: Eligibility criteria

Inclusion criteria
• Patients operated for a hip fracture at Copenhagen University Hospital, Amager-Hvidovre and admitted at the Hip Fracture Unit.
• Age >=60 years
• Ability to speak and understand Danish and with a Danish Social Security Number
• Able to give written informed consent
• Residing at home and with an independent pre-fracture indoor walking ability (NMS≥2)
Exclusion criteria
• Postoperative weight-bearing restrictions
• Multiple fractures
• Active cancer or suspected pathological fracture
• Patients unable/unwilling to cooperate for testing and rehabilitation
• Planned/elective hospitalization within the trial period.
• Cognitive dysfunction determined by chart review, reported by nursing staff or observed by trained research staff (disoriented, dementia, active delirium)
• Uncontrolled blood pressure (systolic > 150 mmHg, or diastolic > 100 mmHg)
• Heart disease in the form of peri-, myo- or endocarditis.
• History of stroke with motor disability.
• Heart failure (NYHA class III and IV)
• Evidence of kidney failure or renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m2 or serum creatinine >200µmol/L)
• Abnormal liver function tests (alanine aminotransferase, γ-glutamyltransferase, bilirubin, or alkaline phosphatase >2 times the upper limit of normal) or history of hepatic tumor.
• Elevated hematocrit ≥ 50%
• History of breast or prostate cancer
• Abnormally elevated serum PSA assessed at the 3-week control* corresponding to PSA < 4.0 µg/L (60–70 years), PSA < 5.0 µg/L (>70 years).
• Allergic to ingredients in the Deca-Durabolin solution (Nandrolone, benzyl alcohol, arachis oil (peanut-oil) and allergy to peanuts or soya) or milk protein allergy (nutritional drink).

* PSA during admittance could be increased due to catherization, therefore PSA will be assessed at 3 weeks and patients excluded at this timepoint if elevated values are identified.
Reprinted from Hulsbæk 2019[95]

Intervention and trial procedures

Participants were randomized (1:1) to: 1. Anabolic steroid or 2. Placebo. Both groups received identical physiotherapy and a nutritional supplement. Table 3 provides a summary of the intervention (full descriptions are available from paper 2+3).

Table 3: Description of intervention

Anabolic steroid	**Active arm (INT):** Nandrolone decanoate (Deca-Durabolin 50mg/ml produced by Aspen). Women: 50 mg Men: Total testosterone ≥ 11 nmol/l = 100 mg. Total testosterone < 11 nmol/l = 200 mg. **Placebo arm (CON):** 1 ml Sodium Chloride 9 mg/ml (produced by Fresenius Kabi). Injections were administered intramuscular every 3 weeks. First injection was administered at baseline and last injection at week 12.
Physiotherapy	**Acute hospital:** Initiated postoperative day 1 and included functional exercises such as transfers and walking, as well as exercise therapy primarily aimed at lower extremities. **Municipality based rehabilitation [a]:** 1 hour twice a week, up to and including the 12th week after inclusion. The training session consisted of warm up, functional training, balance training, lower limb exercises and progressive strength training. *Progressive strength training [b]:* 2 mandatory strength training exercises: (knee-extension and leg press) Standardized protocol with 3 sets of each exercise. Week 0-2: 15 repetitions, intensity of 15 RM Week 3-4: 12 repetitions with 12 RM Week 5-12: 10 repetitions with 10 RM The load was progressed on a set to set basis if possible, at least from session to session. The load, number of repetitions and pain for each set was logged by the PT
Nutritional supplement	2 bottles per day for 12 weeks [c]. The protein-rich nutritional supplement is a liquid containing 18 g milk-based protein pr. bottle (Nestlé Resource 2.0 + fiber).
RM: Repetition maximum, PT: physiotherapist [a] All municipalities including 9 different rehabilitation centers in the catchment area of the hospital participated. [b] The progressive strength training intervention was based on previous studies in hip fracture patients and general recommendations[9,12,97–99]. [c] The protein-rich nutritional supplement was planned to account for at least 35% of the patient's daily protein requirement. The standard used at the hip fracture unit is 1.35 g/kg bodyweight/day.	

Content in the table based on Hulsbæk 2021[96]

Baseline testing was carried out by the PhD student within postoperative day 3-10 and extended over 2 days due to the extensive test battery. Randomization took place after baseline testing and a dedicated nurse (not blinded) administered the first injection of the trial solutions. The participants, outcome assessors, healthcare providers, intervention deliverers, data collectors and analysts were all blinded to group allocation. Weekly telephone calls to the participants were carried out by the PhD student during the entire enrollment period, both to promote and monitor compliance to the intervention but also to detect potential adverse events. Hospital controls were carried out every 3rd week to perform blood tests, assess safety parameters and administer trial

medication. Participants were offered free transportation to both hospital visits and rehabilitation. Figure 3 provides an overview of the trial and the trial related events.

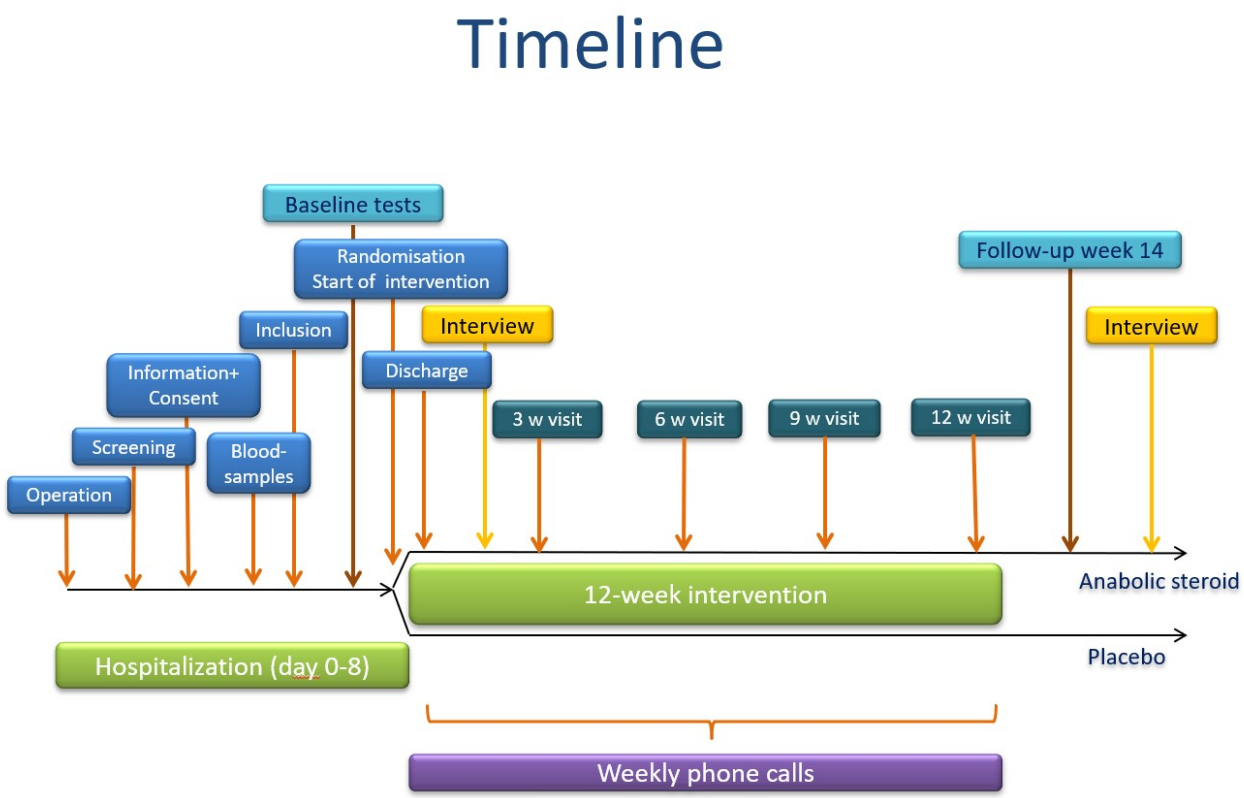

Figure 3: Timeline of trial related events

Outcomes

Feasibility

The following feasibility aspects were assessed: Number of eligible patients, inclusion rate per month, feasibility and suitability of outcome measures, acceptability of the interventions, adherence to the intervention, retention to the scheduled controls and follow-up, and number and severity of adverse events.

Outcomes of effectiveness

Blinded outcome assessment was conducted at baseline and at follow-up by the PhD student. Primary outcome is described below. Secondary outcomes and time of assessment are shown in table 4 and described in detail in paper 2 and 3.

Primary outcome was change in maximal isometric knee-extension strength (Nm/Kg) in the fractured limb from baseline to 14-week follow-up, and it was measured using a belt fixated handheld dynamometer (Commander Muscle Tester; JTech Medical Utah, USA).[6,9,100,101]

The test was conducted following a standardized protocol. The participant was seated at the bedside, with the hips and knee joint angle in 90˚ flexion and the hands placed on the mattress in line with the hips for support. The lever arm length was measured from the lateral epicondyle of the femur to the center of the dynamometer transducer pad, which was placed 4 cm above the lateral malleolus of the tibial bone. Four trials were carried out and the highest value (in Newtons, N) used for analysis. Tests were performed with standardized verbal encouragement.

Safety parameters were assessed at baseline, 3, 6, 9, 12 and 14 weeks, and described in paper 2 and 3. Predefined safety thresholds for 3 safety parameters were as follows: Hematocrit (safety threshold: Values > 0.50); liver tests (safety threshold: If liver test values are >3 times the upper limit of normal); PSA (safety threshold: If PSA increases to more than 50%). If the values exceeded the predefined thresholds the treatment with Deca-Durabolin was discontinued. Moreover, if female participants experienced displeasing androgenic side effects, the treatment was discontinued. Adverse events (AE) and adverse reactions (AR) including an assessment of severity and expectedness was recorded in accordance with European guidelines.[102]

Table 4: Table of outcome assessments

	Study period					
	Allo-cation	**Post-allocation**				**Follow-up**
TIMEPOINT	**0**	t_1	t_2	t_3	t_4	t_5
ASSESSMENTS	**Base-line**	***3 weeks***	***6 weeks***	***9 weeks***	***12 weeks***	***14 weeks***
Feasibility outcomes						
Number of eligible patients, inclusion rate, feasibility/suitability of outcome measures, acceptability, adherence, retention, adverse events.	X	X	X	X	X	X
Performance measures						
Isometric knee-extension strength fractured and non-fractured leg (Nm/kg)	X					X
Max knee-extension strength in the fractured leg in % of non-fractured	X					X
Hand Grip Strength (Kg)	X					X
Gait speed, 10-meter fast walk (m/s)	X					X
Timed Up & Go test, TUG (s)	X					X
De Morton Mobility Index, DEMMI (0-100)	X					X
1-week physical activity (sedentary & upright time, steps, transfers) ActivePAL					X	
Patient reported outcomes						
Mini Nutritional Assessment, MNA-SF (0-14)	X					X
New Mobility Score, NMS (0-9)	X*	X	X	X	X	X
Health-related quality of life, EQ5D-3L / EQ5D-VAS	X*					X
Hip fracture-related pain, Verbal Rating Scale (0-4)	X	X	X	X	X	X
Short Falls Efficacy Scale-I, Short FES-I (7-28)	X					X
Fatigue, SF36 vitality subscale (0-100)	X*	X	X	X	X	X
Geriatric Depression Scale, GDS-15 (0-15)	X*					X
Other outcomes						
Bone mineral density (BMD), Lean body mass (LBM), and total fat mass assed by DEXA-scan	X					X
Total testosterone	X	X	X	X	X	X
Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Sex hormone binding globulin (SHBG)	X	X	X	X	X	X
Lipid profile	X	X	X	X	X	X
C-reactive protein (CRP)	X	X	X	X	X	X
Safety Parameters	X	X	X	X	X	X
*Assessment at baseline but refers to the time-period prior to the fracture						

Modified after Hulsbæk 2019[95]

Sample Size

The sample size calculation was made to detect a between-group difference in the change score for knee-extension strength in the fractured limb of 0.2 Nm/kg in favor of the intervention group. Lehr's formula was used for calculation and a SD of 0.22 Nm/kg retrieved from a previous study.[6] The defined difference in the change scores is larger than what might be considered the minimal clinically important difference, but found acceptable, as this pilot trial aims to explore preliminary effect.[103] Calculations suggested 20 participants in each group using a standard of 80% power and type 1 error rate of 5%. To account for an estimated dropout rate of 20%, target samples size was set to be 48 participants.

Statistical analyses

Baseline characteristics are presented using descriptive statics and feasibility measures are similarly evaluated descriptively. For the sake of simplicity results of primary and secondary outcomes are presented as mean (SD), despite the small numbers in each group. Within-group and between-group differences are reported as means with 95% confidence intervals (CI) and they are analyzed using a 'Two sample t-test' or 'Wilcoxon rank sum test' depended on the best judgement of normality of distribution of the change scores. All randomly assigned participants with data are included in the primary analysis ("available cases", n=21) and it is referred to as modified intention-to-treat analysis. Because of the small sample size, decision was made not to impute missing data. Secondary exploratory per-protocol analyzes were conducted for the primary outcome, excluding participants with less than 75% adherence to training sessions and 80% received injections. Per-protocol analyses based on nutritional intake was not conducted due to the low intake. In this thesis further descriptive analysis was made to evaluate the patient's recovery of function and HRQoL. The level of significance was set at $p<0.05$

Study 3

The following section is based on paper 4 (manuscript in the appendix).

Design and population

The qualitative study was nested within the pilot RCT and applied an explorative descriptive design. The sampling strategy was consecutive, as all randomized participants were invited to participate in interviews. The formalities for undertaking interviews were first established at the time of including participant ID9. Therefore, participants from ID9 and onwards were invited to take part in baseline interviews, while all participants were invited for follow-up interviews.

Data collection

We conducted semistructured telephone interviews at baseline (1-2 weeks after enrollment) and follow-up (within 3 weeks after trial termination). The PhD student undertook baseline interviews and follow-up interviews was conducted by a second investigator (LBL) not otherwise involved in the trial. Two semistructured interview guides were constructed to guide the interviews (Paper 4, Appendix). The baseline interview focused on the participants perspectives and motivation for engaging in the clinical trial involving anabolic steroids in rehabilitation. Follow-up interviews focused on the participants evaluation of participating in the trial, fulfillment of their expectations and suggestions for adjustments.

Data analysis

The audio recorded interviews were transcribed verbatim in an anonymized form. Baseline interviews were transcribed by the PhD student, and follow-up interviews were transcribed by a trained transcriptionist. Content analysis with a sequential model of deductive and inductive development of categories was undertaken to develop descriptions of the participants' motivations for and evaluation of participating in the trial.[104,105] Firstly, deductive categories based on the study aim and interview guide was applied as a framework to structure the content and assist the coding. Secondly, an inductive process of reorganizing categories and establishing new categories were undertaken. To get immersed in the data and obtain a sense of the whole [104] all data was read several times by the PhD student and LBL. The 2 researchers coded all interviews simultaneously and consensus on the coding was reached immediately by discussion. Consensus meetings and investigator triangulation including all the involved researchers was held at each stage of the analysis process, discussing codes and categories, which eventually lead to a final agreement on the overarching categories and sub-categories.

Results

In the below section a summary of results from the 3 studies are presented. For a detailed description please see the specific papers 1, 3 and 4 in the appendix.

Study 1

The following section is based on paper 1.[90]

Selection and characteristics

The literature search resulted in 6093 hits, and after removal of duplicates 3802 was left for title and abstract screening. Ninety-five studies was screened in full text, which resulted in inclusion of 49 studies[6,10,11,106–151] in the review (equivalent to 54 study comparisons, as some studies had 3 or 4 arms). Relevant data for pooling in the quantitative analysis was not available in 5 studies[114,131,139,147,148], leaving 44 studies for the meta-analysis (49 comparisons). Flow of the study selection process are illustrated in figure 4.

A total of 3905 participants was included in the 49 studies. Demographics and study characteristics are presented in paper 1 (supplementary eTable 1). The included studies had sample sizes ranging from 20 to 304 and were carried out in 20 different countries. The average age of the study participants was 80.6 years (range 73-85 years) and the proportion of women was 79,6% (range 59.5-100%).

Risk of bias of the effect estimates in the included studies are illustrated in paper 1 (supplementary eTable 2). For the objective outcome measures only one study was rated as low risk of bias, 27 as ‘some concerns’ and 20 at high risk of bias. For the patient reported outcomes no effect estimates were rated as low risk of bias, 18 were rated ‘some concerns’, and 15 at high risk of bias. Quality assessment of the body of evidence using the GRADE approach is presented in ‘the summary of findings table’ paper 1, table 1.

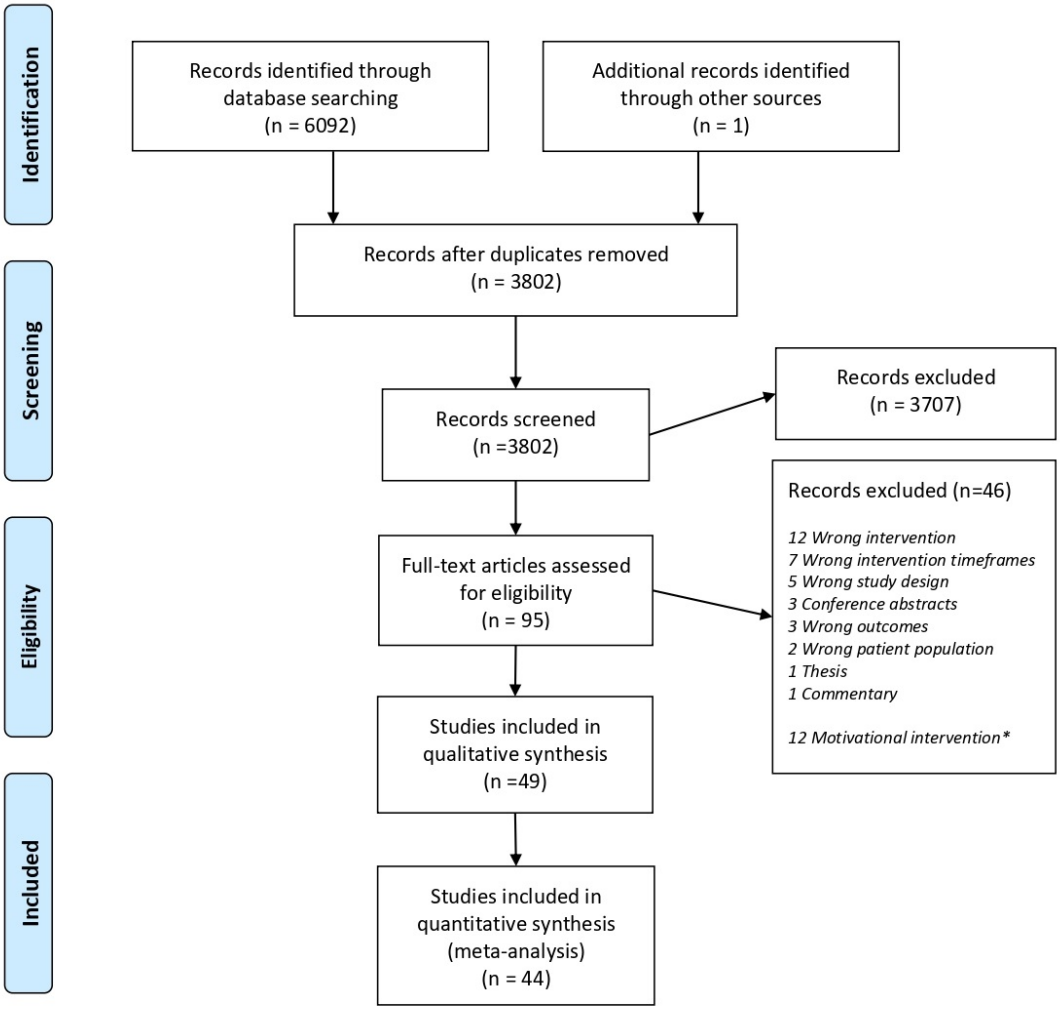

Figure 4: Study flow diagram *(Reprinted from Hulsbæk 2021[90] with permission from Oxford University Press).*

Mobility

Thirty-three studies were included in the analysis of mobility (2754 participants). A moderate positive effect of exercise therapy on mobility was indicated at short-term follow-up SMD 0.49 (95%CI 0.22 to 0.76) but showed considerable heterogeneity I^2=90.94% (figure 5+6). Using the GRADE approach, the overall evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Subgroup analyses are presented in figure 7 and suggested a statistically significant effect (p=0.04) for 'Modality of intervention', indicating a statistically significant moderate effect of functional exercises on mobility (SMD 0.58, 95%CI 0.22 to 0.94, I^2=87.22), and strength training with an insignificant but large effect on mobility (SMD 0.74, 95%CI -0.05 to 1.52, I^2=95.48).

Fifteen studies (1185 participants) provided data on long-term follow-up for mobility. A large statistically significant effect of SMD 0.74 (95%CI 0.15 to 1.34) was identified, but with considerable heterogeneity of I^2=95.47% (figure 5 and paper 1, supplementary eFigure 1).

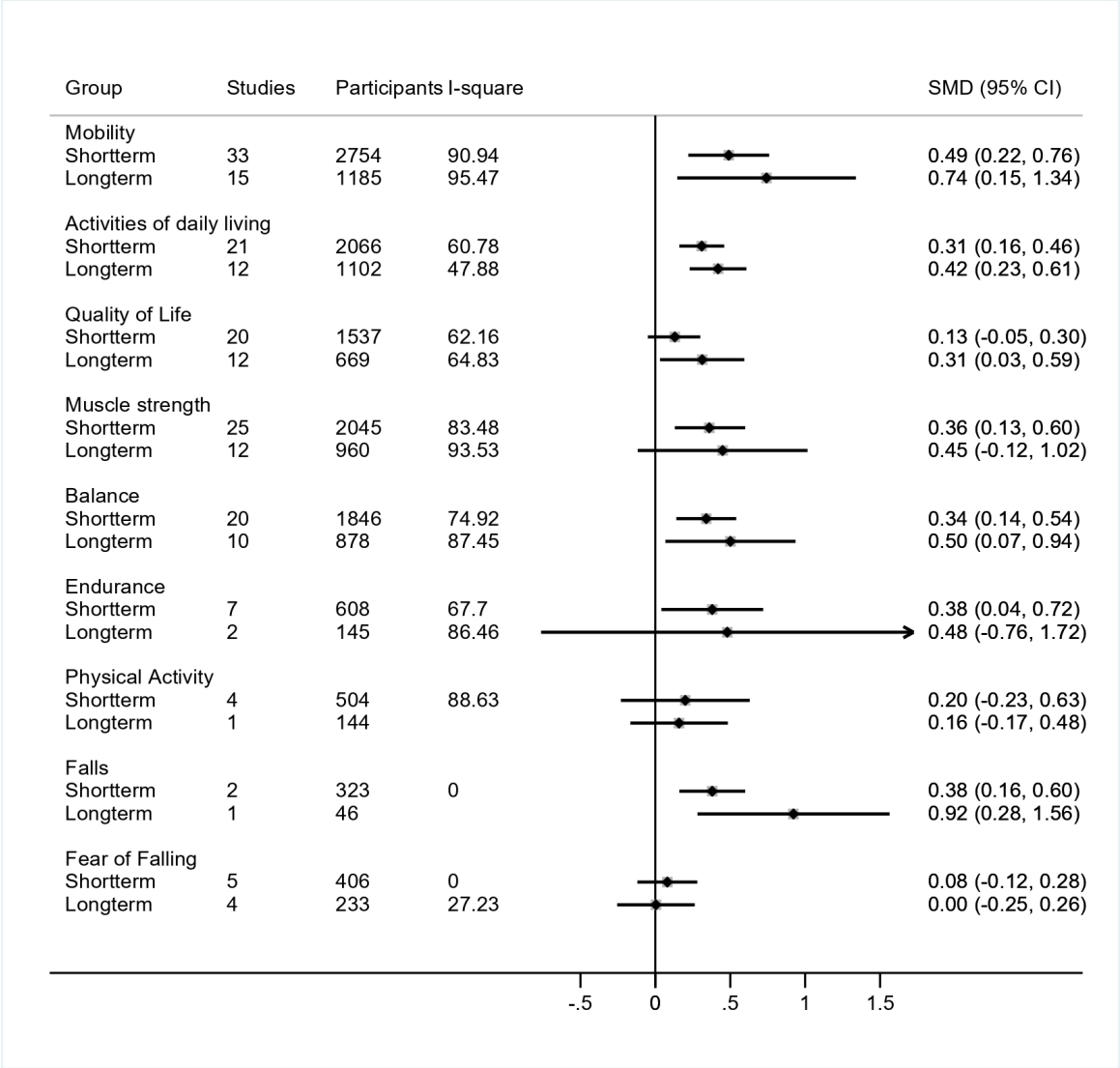

Figure 5: Forrest plots overview of the effect of exercise therapy on selected outcomes at short- and long-term follow-up after hip fracture.
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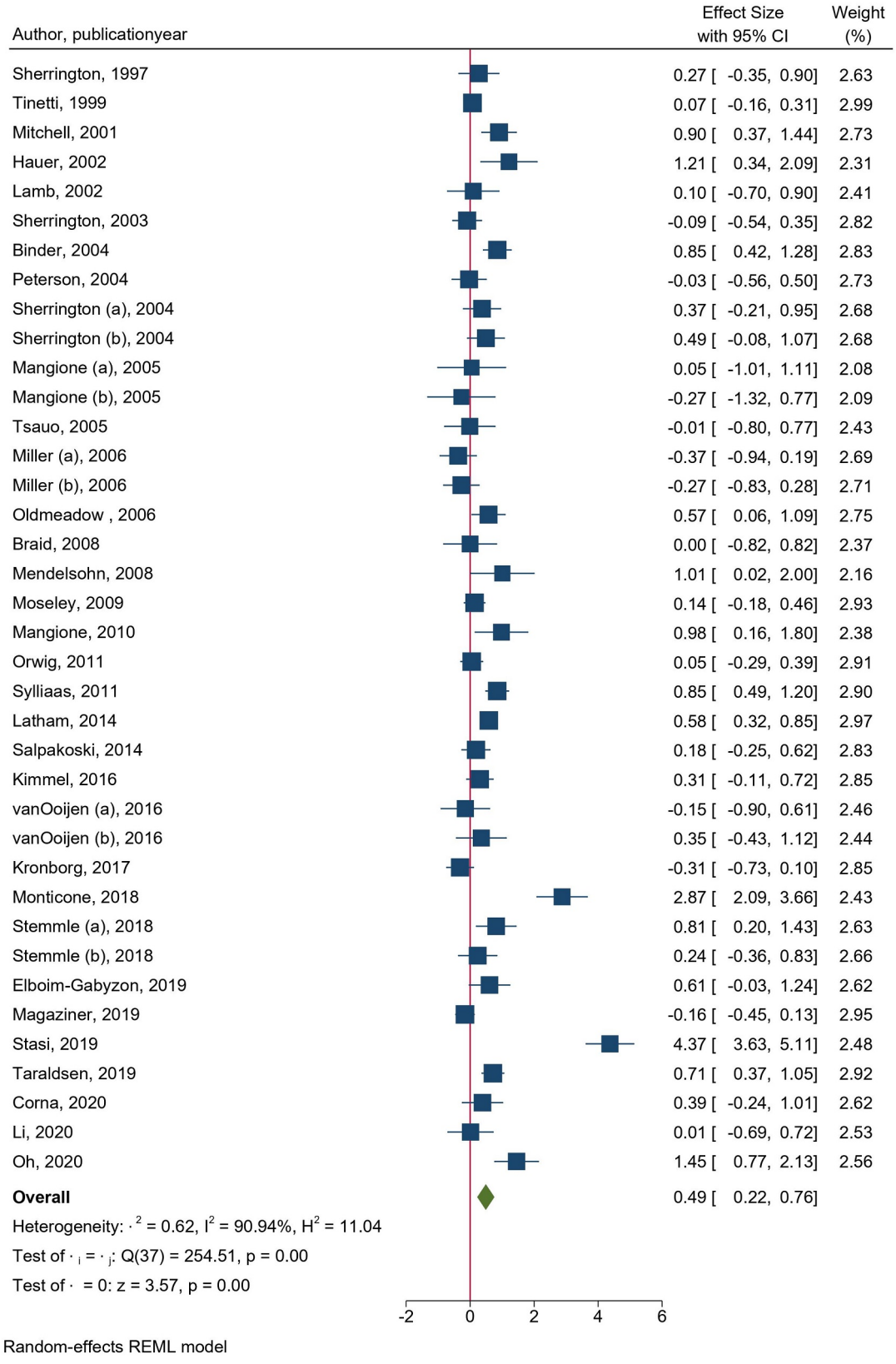

Figure 6: Forest plot of the effect of exercise therapy on mobility at short-term.
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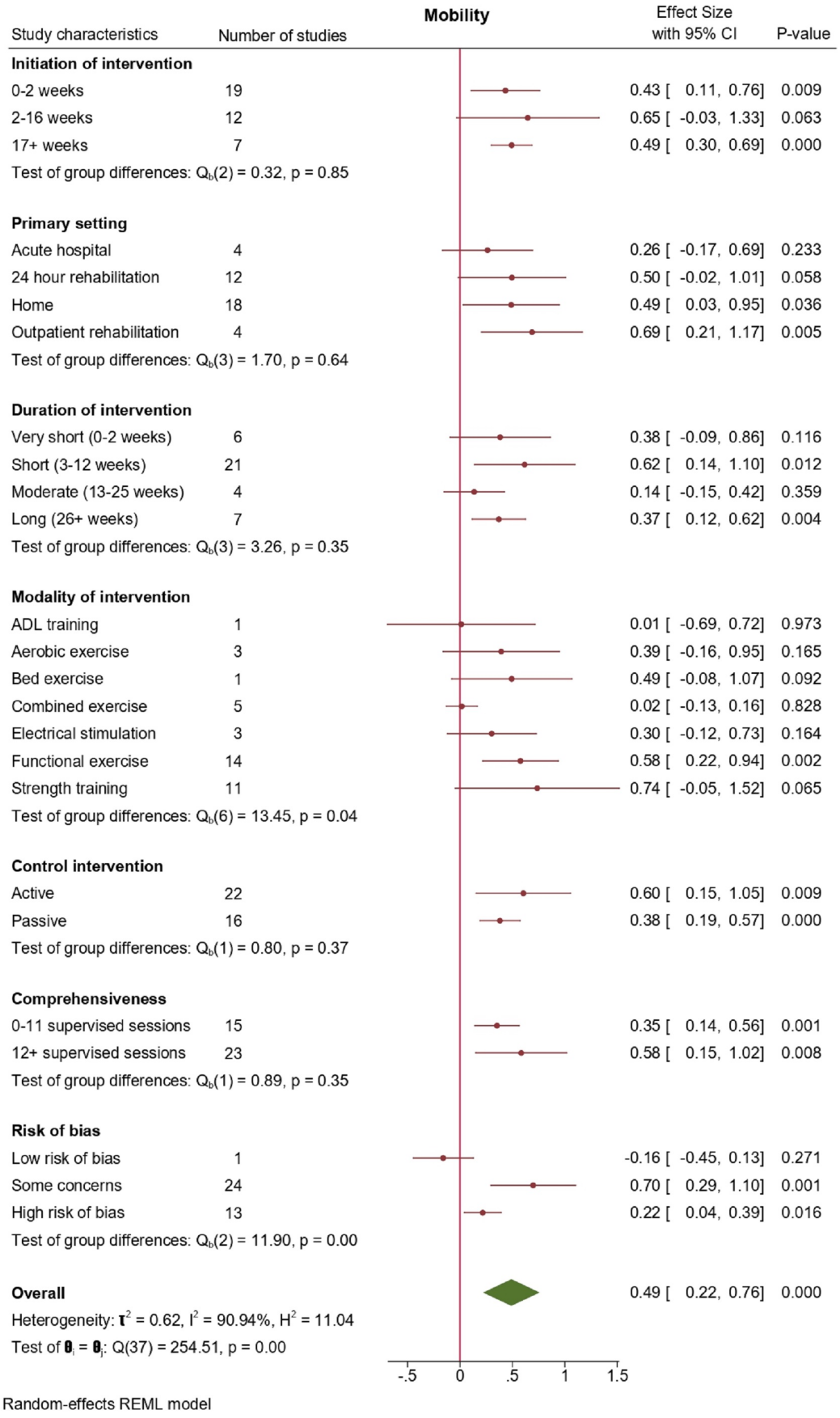

Figure 7: Subgroup analysis of the effect of exercise therapy on mobility.

ADL

At short-term 21 studies (2066 participants) contributed with data, and the meta-analysis showed a statistically significant effect of exercise therapy (SMD 0.31, 95%CI 0.16 to 0.46, I^2=60.78%) on ADL (figure 5 and paper 1, supplementary eFigure 2). The overall evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Subgroup analyses for ADL at short-term are presented in paper 1 (supplementary eFigure 3). Findings suggested that the effect of the interventions was modified by: Primary setting (p=0.01), with largest effect size for acute hospital (SMD 0.62, 95%CI 0.38 to 0.85, I^2=64.65); Duration of intervention (p=0.01), with largest effect for very short interventions 0-2 weeks (SMD 0.66, 95%CI 0.38 to 0.94, I^2=19.25); Modality of intervention (p<0.001), with significant effect for ADL training (SMD 0.59, 95%CI 0.31 to 0.87, I^2=14.63); Comprehensiveness of intervention (p=0.01) with largest effect for less comprehensive intervention of 0-12 supervised sessions (SMD 0.53, 95%CI 0.34 to 0.73, I^2=22.50); Risk of bias (p=0.01), largest effect for studies classified as "some concern" (SMD 0.53, 95%CI 0.34 to 0.73, I^2=52.10).

Twelve studies investigated long-term effect of exercise therapy on ADL (1102 participants). A statistically significant moderate effect was found (SMD 0.42, 95%CI 0.23 to 0.61, I^2=47.88%) (figure 5 and paper 1, supplementary eFigure 4).

HRQoL

Twenty studies reported on HRQoL at short-term follow-up (1537 participants). The meta-analysis indicated no statistically significant effect of exercise therapy on HRQoL (SMD 0.13, 95%CI -0.05 to 0.30, I^2=62.16%) (Figure 5 and paper 1, supplementary eFigure 5). The overall evidence was judged as low with downgrading due to study limitation and inconsistency.

Stratified analyses showed no statistically significant effect modification for any of the subgroups (paper 1, supplementary eFigure 6).

Long-term effects of HRQoL were investigated including data from 13 studies (669 participants), and a statistically significant small effect was identified (SMD 0.31, 95%CI 0.03 to 0.59, I^2=64.83%) (figure 5 and paper 1, supplementary eFigure 7).

Lower limb muscle strength

Lower limb muscle strength was reported in 25 studies (2045 participants) at short-term. A statistically significant effect was identified (SMD 0.36, 95%CI 0.13 to 0.60, I^2=83.48%) (figure 5 and paper 1, supplementary eFigure 8). The overall body of evidence was judged as low with downgrading due to study limitation and inconsistency. Subgroup analyses are illustrated in paper 1 (supplementary eFigure 9). Effect modification was shown for intervention modality

(p=0.07) with a statistically significant effect of strength training (SMD 0.72, 95%CI 0.27 to 1.18, I^2=87.37). For the long-term effect of exercise therapy on lower limp muscle strength 12 studies (960 participants) were included in the analysis, and a statistical non-significant moderate effect was identified (SMD 0.45, 95%CI -0.12 to 1.02, I^2=93.53%) (figure 5 and paper 1, supplementary eFigure 10).

Balance

20 studies (1846 participants) were included in the analysis of the effect of exercise therapy on balance at short-term. A small but statistically significant effect was identified (SMD 0.34, 95%CI 0.14 to 0.54, I^2=74.92%) (figure 2 and paper 1, supplementary eFigure 11). The overall evidence was judged as low with downgrading due to study limitation and inconsistency. Subgroup analyses illustrated effect modification by setting, duration of intervention and modality (functional exercise and strength training having significant moderate effect sizes (SMD 0.45, 95%CI 0.01 to 0.89, I^2=84.76 and SMD 0.57, 95%CI 0.26 to 0.87, I^2=46.78 respectively) (paper 1, supplementary eFigure 12). At long-term 10 studies (878 participants) were included in the analysis and showed a statistically significant moderate effect (SMD 0.50, 95%CI 0.07 to 0.94, I^2=87.45% (figure 5 and paper 1, supplementary eFigure 13).

Other outcomes

The short-term effect of endurance, physical activity, falls and fear of falling are shown in figure 5 and paper 1, supplementary eFigure 14-17.

Small sample bias

Funnel plots and eggers test did not show signs of small sample bias for mobility, ADL, HRQol, muscle strength and balance (paper 1, supplementary eFigure 18-22).

Study 2

The below section is based on paper 3.[96]

Feasibility

Out of 717 screened patients, 29 were included and 23 randomized (figure 8). The total inclusion period was 16.5 months, corresponding to an inclusion rate of approximately 1.8 patients per month (inclusion was discontinued for 23 weeks due to the PhD student's absence related to course participation and holidays).

Reasons for non-eligibility are presented in paper 3 (supplementary eTable 1) and the two most frequent reasons were "not home-dwelling" (18%) and "cognitive dysfunction" (16%). The number of patients that were eligible, but declined to participate was 41, with the most frequent reason to decline participation being "Overwhelmed and stressed by situation" (37%) (paper 3, supplementary eTable 2).

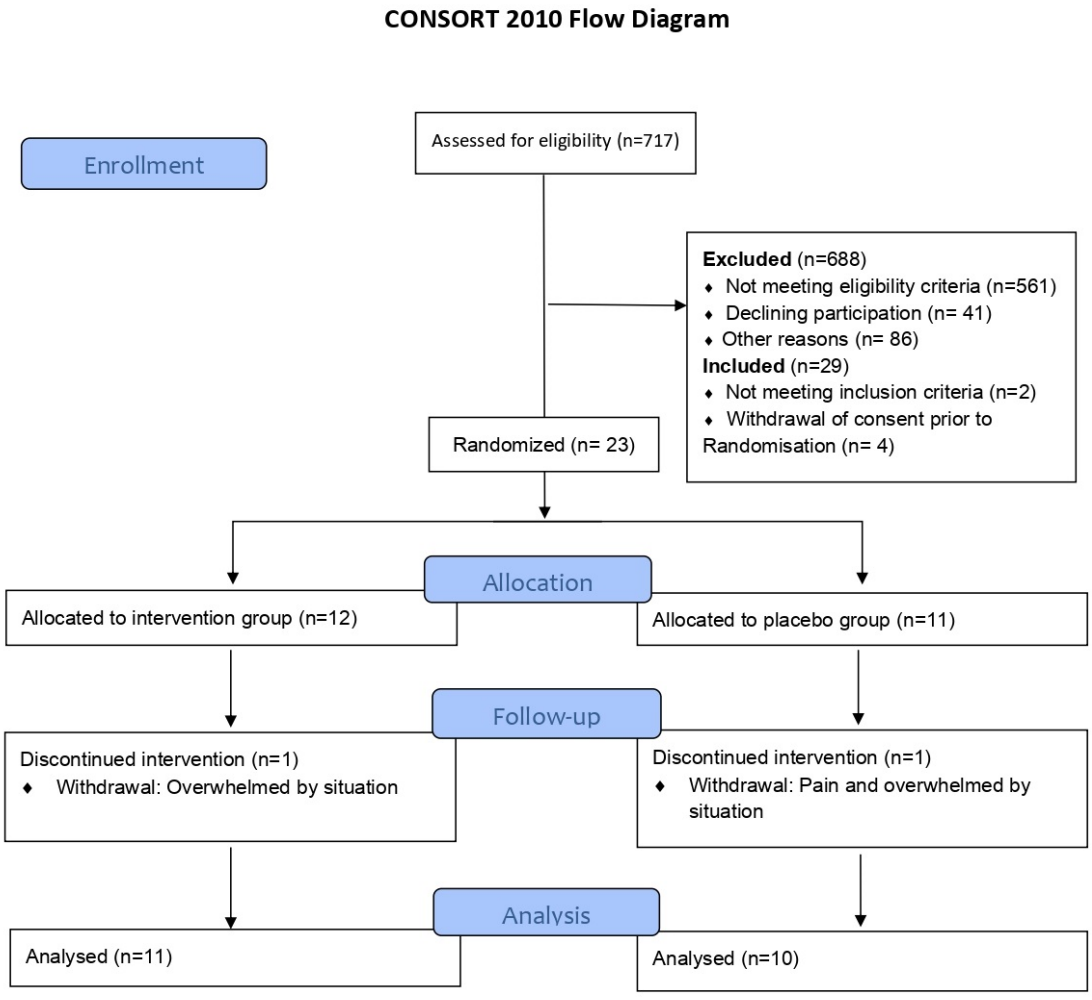

Figure 8: Participant flow chart *(Reprinted from Hulsbæk 2021[96]).*

Baseline characteristics are presented in paper 3, table 1. The mean age of the randomized participants was 73.4 (6.7) years and 78 % were women. In comparison, the mean age of 717 screened patients were 78.3 (12.2) years with 66% women. Participants in the trial generally had a high pre-fracture functional level, with 91% being discharged to their own home after median 8 (7-9) days of hospitalization. No significant baseline differences were identified between the intervention group and control group.

Adherence

Medication: Adherence to injections was 87% (see box 1).

Exercise: Adherence to the municipality-based physiotherapy was 91% out of the offered sessions. The participants exercised in 8 different rehabilitation centers placed in the catchment area of the hospital. The Covid-19 lockdown caused 3 participants to discontinue the planned municipality-based exercise intervention. The remaining 18 participants were offered an average of 21.3 (2.3) exercise sessions.

The adherence to the progressive strength exercises was good. Five participants paused the knee-extension exercises due to pain for 1 to 4 sessions, simultaneously two of these participants also paused leg press exercise. The progression in training loads seemed sufficient within the different RM levels for both the knee-extension exercise for the fractured leg (figure 9) and for leg-press exercise (paper 3, supplementary, eTable 3). The load progression during the first 2 weeks was calculated from the 2nd to the 4th session, because load-values varied a lot in the first session, as the physiotherapist had to identify the right load-level.

Box 1: Overview of reasons for non-adherence to injections

5 INT	1 stopped after 2 injections: Covid-19, risk of getting infected by contact to hospital staff. 1 stopped after 2 injections: Myocardial infarction, pre-existing coronary stenosis (classified non-related). 1 stopped after 2 injections: Increased liver parameters (classified potentially related). 1 stopped after 3 injections: Increased perspiration and facial hirsutism (classified potentially related). 1 missed 1 injection: Slightly increased PSA value (classified potentially related).
1 CON	1 stopped after 3 injections: Increased liver parameters (classified potentially related).

Content from Hulsbæk 2021[96]

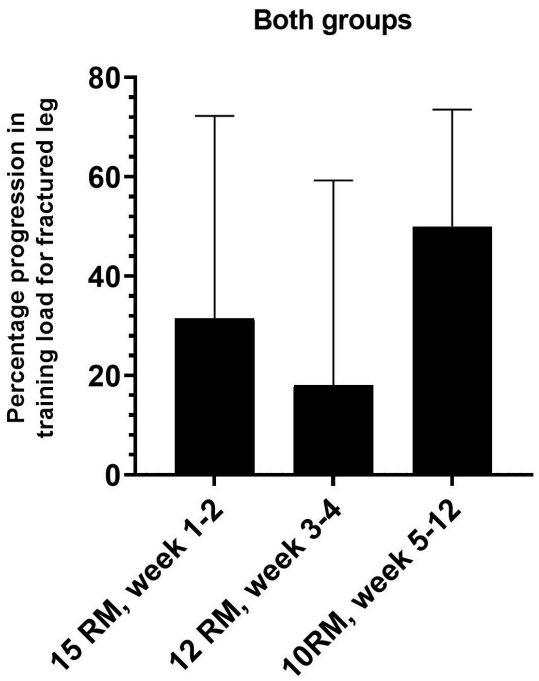

Figure 9: Percentage progression in training load for fractured leg knee extension strength, both groups (median, q3).

Nutritional supplement: 61 % of the planned 168 drinks was consumed, with no significant between-group difference (INT 58.5% vs CON 63.4%). The most frequently reported reason for non-consumption was loss of appetite, nausea, dislike taste and reflux.

Hospital controls: Adherence to hospitals controls were excellent. Due to Covid-19 lock-down, 1 participant did not attend 3 scheduled controls.

Feasibility of outcome measures: High completeness of data for all outcome measures suggest that they were feasible to perform during the timeframe of the study in this better functioning group of hip fracture patients. However, the many measurements were time-consuming and exhausting to the participants at baseline, consequently testing took place over two days. Likewise, DEXA-scanning at baseline was challenging for participants, as they were restricted by pain and limited mobility. The geriatric depression scale had overlapping content with EQ5D that also covers depression and anxiety and the EQ5D would have been sufficient.

Primary outcome

Significant within-group improvements from baseline to follow-up were seen for knee-extension strength in the intervention group for both the fractured and non-fractured leg and in the control group for the fractured leg (table 5). An insignificant between-group difference of 0.11 (95%Cl -0.25;0.48) Nm/kg was identified for the fractured leg in favor of the intervention group. The corresponding median percentage change in knee-extension strength for the fractured leg was

178% (41-263) for the intervention group and 50% (20-173) for the control group (p=0.28) as shown in figure 10. The between-group difference for the non-fractured leg was insignificant 0.16 (95% CI -0.05;0.36) Nm/Kg in favor of the intervention group. The percentage change in knee-extension strength of non-fractured leg was median 31% (12-53%) for the intervention group and 8% (0-33) for the control group (p=0.04).

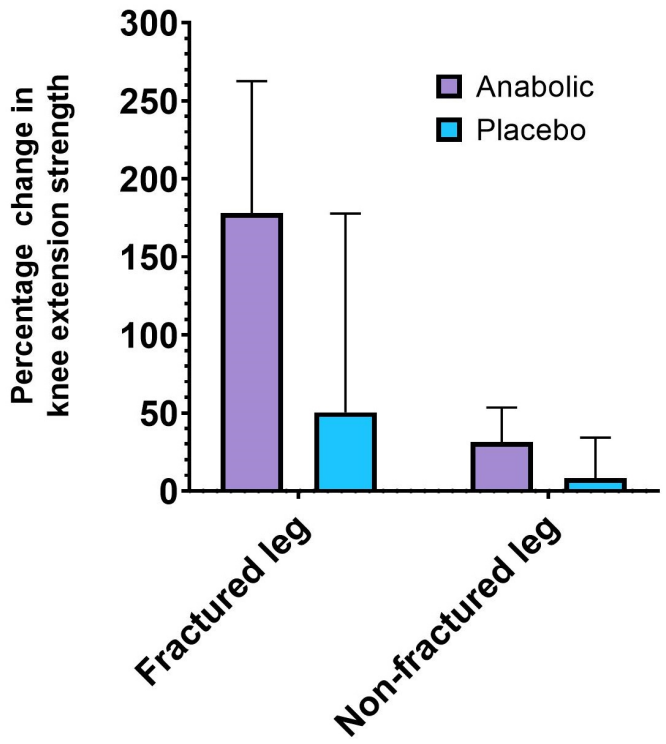

Figure 10: Percentage change in knee extensions strength of fractured and nonfractured leg for each group (median, q3).

Table 5: Analyses of primary outcome, knee-extension strength (n=21)

Primary outcome	Baseline Mean (SD)		Follow-up Mean (SD)		Within-group difference Mean (95% CI)		Between-group difference Mean (95% CI)
Modified intention-to-treat							
	INT (n=11)	**CON (n=10)**	**INT (n=11)**	**CON (n=10)**	**INT (n=11)**	**CON (n=10)**	
Strength, Fractured (Nm/kg)	0.56 (0.38)	0.72 (0.36)	1.17 (0.46)	1.23 (0.39)	0.61 (0.34;0.88)	0.50 (0.21;0.79)	0.11 (-0.25; 0.48)
Strength, non-fractured (Nm/kg)	1.07 (0.45)	1.27 (0.26)	1.35 (0.39)	1.40 (0.39)	0.28 (0.20;0.37)	0.13 (-0.07;0.32)	0.16 (-0.05; 0.36)
Strength, fractured % non-fractured (%)	50.5 (21.6)	59.4 (31.0)	84.6 (15.4)	89.1 (16.2)	34.1 (16.5;51.6)	29.7 (9.0;50.3)	4.4 (-20.7; 29.5)
Per protocol							
Exercise[a]	**(n=8)**	**(n=10)**	**(n=8)**	**(n=10)**	**(n=8)**	**(n=10)**	
Strength, Fractured (Nm/kg)	0.62 (0.42)	0.73 (0.37)	1.35 (0.40)	1.23 (0.39)	0.72 (0.42;1.03)	0.50 (0.21;0.79)	0.23 (-0.16; 0.61)
Strength, non-fractured (Nm/kg)	1.15 (0.50)	1.27 (0.26)	1.45 (0.40)	1.40 (0.39)	0.29 (0.19;0.40)	0.13 (-0.07;0.32)	0.17 (-0.04; 0.37)
Injections	**(n=7)**	**(n=9)**	**(n=7)**	**(n=9)**	**(n=7)**	**(n=9)**	
Strength, Fractured (Nm/kg)	0.36 (0.17)	0.69 (0.37)	1.14 (0.45)	1.25 (0.40)	0.78 (0.47;1.09)	0.56 (0.26;0.85)	0.22 (-0.17;0.61)
Strength, non-fractured (Nm/kg)	1.00 (0.48)	1.29 (0.26)	1.33 (0.39)	1.39 (0.41)	0.33 (0.23;0.42)	0.10 (-0.11;0.31)	0.22 (0.01;0.44)[*]
Exercise + injections	**(n=5)**	**(n=9)**	**(n=5)**	**(n=9)**	**(n=5)**	**(n=9)**	
Strength, Fractured (Nm/kg)	0.38 (0.17)	0.69 (0.37)	1.27 (0.48)	1.25 (0.40)	0.89 (0.49;1.29)	0.56 (0.26;0.85)	0.34 (-0.10;0.77)
Strength, non-fractured (Nm/kg)	1.05 (0.57)	1.29 (0.26)	1.36 (0.47)	1.39 (0.41)	0.32 (0.18;0.46)	0.10 (-0.11;0.31)	0.22 (-0.07;0.50)

Note: INT=intervention (anabolic group), CON=control group.
Note: Cases removed if adherence below 75% for exercise (pre-defined) and 80% for injections.
[a] 3 participants non adherent to exercise due to Covid-19 lock-down.
[*] P=0.046 (Sattertwaite due to unequal variance)

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Secondary outcomes

The median increase in plasma testosterone for the intervention group was 3.9 (IQR, 1.2;7.5) nmol/l and for the control group median 0.15 (IQR, 0;0.40) nmol/l, corresponding to a between-group difference of 3.7 nmol/l (p=0.04, Wilcoxon rank sum test). No statistically significant differences were identified for any other secondary outcomes. The results of the secondary outcomes are presented in paper 3 (supplementary eTable 4). Further, analysis exploring

recovery of pre-fracture function evaluated by the NMS showed a full recovery for 17 out of 21 participants equal to 81% at follow-up. Correspondingly, 57% reported a similar or better HRQoL score at follow-up evaluated by EQ5D-VAS.

Adverse events

A total of 57 adverse events were registered (INT=27, CON=30), out of those three were categorized as serious (1: Myocardial infarction (the participant had preexisting coronary stenosis, and was subsequently treated with stent), 2: Hospital readmission for 24 hours due to hip fracture-related pain, 3: Extended hospitalization because of surgical wound infection. Out of the 57 adverse events, 18 was categorized as potentially related (adverse reactions) see table 6, and 39 categorized as non-related (paper 3, supplementary eTable 6).

Table 6: Adverse reactions by group [a]

Event	INT	CON
Increased lever parameters	1	2
Increased cholesterol parameters (+triglyceride)	3	2
Increased sweating	1	1
Nausea	1	1
Edema + (foot ulcer, upper side from edema)	1	
Rasch		1
Increased PSA	1	
Hirsutism	1	
Increased blood pressure	1	
Increased libido		1
Total	10	8
[a] Categorized as potentially related to anabolic steroid prior to un-blinding.		

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Study 3

The following section is based on paper 4 (manuscript in appendix).

A total of 19 participants engaged in interviews either at baseline (n=14) or follow-up (n=17) or both. The average age of participants was 73 years (range: 62-85 years), 16 were women and 3 men. Participant characteristics are displayed in paper 4, table 1.

The analysis resulted in two overarching categories regarding 'Motivation for enrollment' and 'Evaluation of participation' and seven sub-categories, see figure 11. In the below a summary of the findings are described.

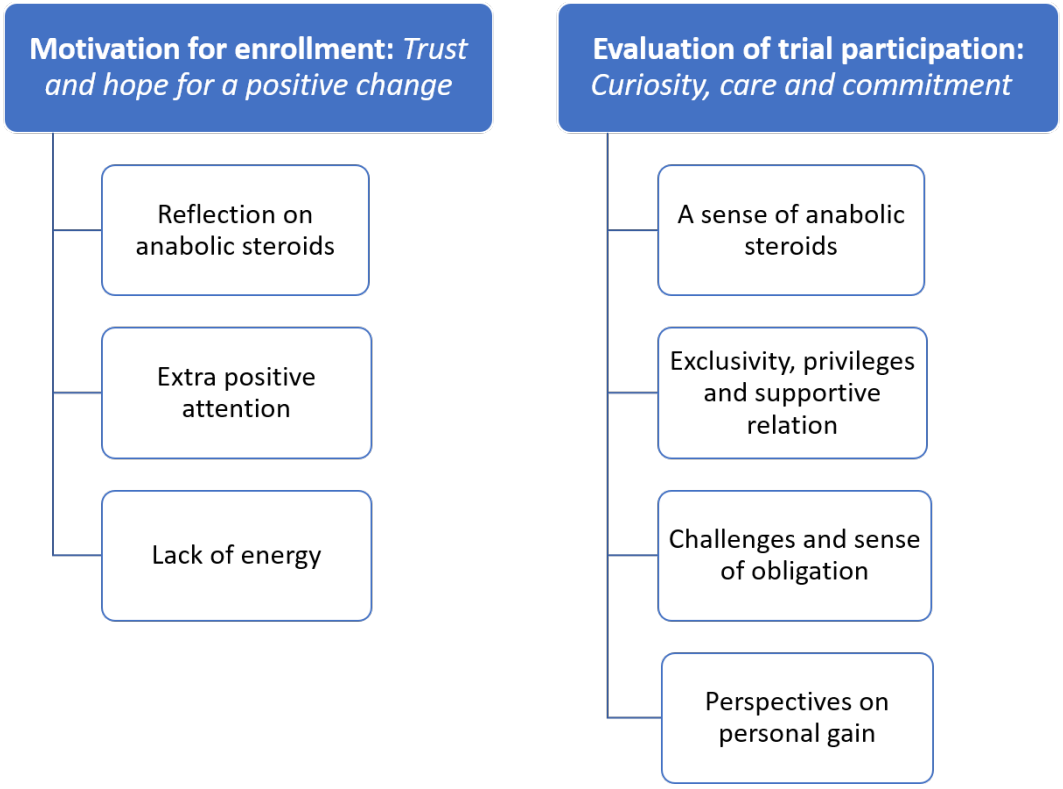

Figure 11: Overview of overarching categories with sub-categories

Trust and hope for positive change (Motivation for enrollment)

Participants generally described few, if any specific expectations, towards their engagement in the trial. They expressed little knowledge of anabolic steroid, and the injections were not a major concern. Some agreed to join the trial for altruistic reasons wanting to help science and future generations. Further, the opportunity to be monitored more closely through extra assessments and hospital controls were also perceived as a motivational factor for participation.

Some participants expressed the early recruitment timepoint (few days post-surgery) as a barrier for engaging in the study, as they felt distressed about the situation and felt a lack of energy and therefore had doubts about their ability to engage in the trial.

Overall participants expressed a noticeable trust, in the purpose of the study and the study staff. Minor worries were overruled by an anticipation of benefits. Moreover, participants expressed a hope that trial participation might lead to a faster recovery and return to life as they knew it before the fracture.

Curiosity, care and commitment (Evaluation of trial participation)

Participants expressed excitement, curiosity and bodily sensations regarding the possibility that they had received anabolic steroids. Those experiencing adverse events, which they speculated could be related to the anabolic steroid, downplayed it, as of minor significance and emphasized the positive experiences of participation in the trial.

Participants expressed a notion of trial participation giving extra privileges. Their narrations reflected gratitude and appreciation of the extra hospital controls, both as they felt thoroughly checked and reassured, but also because of the support and care they received from the project coordinator (PhD student) having the weekly telephone contact. The same feeling of getting something extra applied for the municipality-based physiotherapy intervention, as participants felt they got a more effective training in form of the individualized supervised strength exercises, and not 'just' the standard group exercises offered to peer patients participating in the group exercise (whom were not involved in the trial). Further, the participants described that the physiotherapists provided support, cheering and adequate challenge, which was perceived motivating and also resulted in the participants feeling committed to the exercise intervention. Although strength training was regarded as challenging and strenuous, it was also seen as necessary part of recovery, and it was by some perceived to be the 'active ingredient' enhancing strength and accelerating recovery.

The same feeling of commitment also applied for the protein rich nutritional supplement. Many participants disliked the drinks and consuming the planned amount was a major challenge and associated with a feeling of guilt when not possible. Others appreciated the drinks, in particular that they were provided for free, and they were perceived as a good supplement during the first weeks at home, when preparing meals was difficult. Free transportation to the hospital and rehabilitation centers was described as essential for trial participation, although waiting time could be challenging and inconvenient especially in the early phase after surgery.

It was further suggested by participants that their personal outlook might have influenced their attitudes and actions during the trial e.g. awareness of keeping active, making an effort to assume daily activities and pushing themselves beyond their comfort zone. Overall participants appreciated participating in the trial and expressed a wish to continue exercising after trial completion. Many had already signed up for exercise in the community or otherwise made plans to continue exercising.

Discussion

This PhD thesis is based on three studies with three different study designs and with an overall aim of investigating the current knowledge of the effectiveness of exercise therapy after hip fracture surgery, and further to explore a new multimodal intervention adding anabolic steroid to physiotherapy and nutrition in rehabilitation after hip fracture surgery.

Key findings

Study 1: The systematic review indicated low certainty evidence for a small to moderate effect of exercise therapy at short-term follow-up on mobility, ADL, lower limb muscle strength, balance, endurance, and falls. At long-term follow-up the effect of exercise therapy was sustained for mobility, ADL, balance, and falls, and a small significant effect was identified for HRQoL. Subgroup analyses on short-term outcomes indicated which intervention modalities there seemed to modify the effect of exercise therapy. As such, it seemed that strength training improves strength, ADL-training improves ADL and both functional training and strength training improves mobility and balance. Across outcomes large unexplained heterogeneity was present, and therefore results should be interpreted with caution.

Study 2: The pilot RCT showed substantial difficulties recruiting older patients during the acute hospital admission, which seemed to be a major limitation in the current trial design. On the contrary, high adherence to injections 87% and exercise 91% was demonstrated, indicating excellent acceptability of the intervention. Preliminary effect could not be established due to the small sample size, but promising tendencies were seen for the addition of anabolic steroid on the primary outcome of knee-extension strength.

Study 3: The qualitative study indicated that participants had few expectations and were rather carefree and trustful regarding trial participation. They based their motivation for enrollment on altruism, and an assumption that the intervention would do ‘more good than harm’. Participants appreciated the extra attention and support by the health professionals. They explained being curious about the possibility of having received anabolic steroid and valued the access to a more intensive exercise program. Especially, the individualized progressive resistance training was perceived as challenging, but also a key ingredient of their recovery. Further, participants felt committed to the trial making an effort to adhere to trial elements.

Effect of exercise therapy in context of existing evidence

The systematic review (study 1) included 49 studies with 3905 participants and is to the best of my knowledge the largest systematic review investigating the effect of exercise therapy following hip fracture. It delivers an updated quantitative synthetizes of the effect of exercise therapy at both short- and long-term on 9 outcomes relevant for patients and clinicians. The broad scope of the meta-analysis induced statistical heterogeneity and contributes to downgrading of the body of evidence.

The findings of a moderate effect of exercise therapy on mobility is in line with a previous meta-analysis (including 14 studies) finding a small significant effect of structured exercise.[68] Thus, it establishes the importance of exercise therapy to enhance mobility not only at short-term but also at long-term following hip fracture. Subgroup analyses indicated that functional exercise (including balance training) and strength training had the largest impact on mobility, which confirms previous findings suggesting significant effects of strength training[68,70] and balance training[71] on mobility. Concordantly, our findings of a small to moderate effect of exercise therapy on the outcomes of balance and lower limb strength are in correspondence with previous findings.[68,73,74] Similarly our findings support previous findings of strength training being effective in improving lower limp strength and balance[70] and functional training (including balance training) effective in improving balance.[71]

A small to moderate significant effect of exercise therapy on ADL measures was identified at short-term and sustained at long-term follow-up, which substantiates previous findings.[70,74,152] Subgroup analyses suggested, that ADL training but also strength training seemed to impact ADL, which is supported by previous research indicating a small effect of strength training on ADL[70] and an insignificant moderate effect of ADL training on ADL.[71]

We did not find a significant effect of exercise therapy on HRQoL at short-term follow-up, but a small significant effect was identified at long-term. In correspondence, previous reviews of exercise interventions correspondingly showed no significant effect on HRQoL.[74,153] It seems, HRQoL might be influenced by many different factors, and as such is insensitive to exercise interventions alone. However, a delayed effect, as indicated in this study might be present.

Findings suggest trends of larger effect sizes for the interventions carried out in outpatient settings and for interventions being more comprehensive (12+ supervised sessions) for the outcomes of mobility, muscle strength and to some degree balance. This indicates, that supervision and number of supervised sessions might be an important factor, possibly as it promotes adherence and intensity in the exercise interventions, which is also supported by

previous studies, indicating larger effect sizes for supervised exercise intervention compared to non-supervised interventions.[68,73] In contrast, for the outcome ADL it seemed that short to very short interventions during acute hospitalization and inpatient rehabilitation and a less comprehensive intervention (0-11 supervised sessions) was most efficient in improving ADL. Explanations could be that the largest deficits in ADL are present during the acute hospitalization,[154,155] and measurement scales (e.g. Barthel Index) presents with adequate scale width during this timepoint,[154] but shows signs of ceiling effect, particular in patients with higher levels of function, when applied for measurement of ADL after returning to the community.[9,12]

Risk of bias in the effect estimates were 'high' or 'some concerns', only one study was categorized with low risk of bias. In the subgroup analyses across all the outcomes, results suggested that studies assessed to have 'some concerns' showed larger effect sizes compared to the effect sizes in studies assessed to have high risk of bias in the effect estimates. This indicates that we should be less concerned with high risk of bias impacting the effect sizes.

Factors that could potentially influence on the lack of effect in some studies are suboptimal intensity and low adherence. Intensity of the exercise interventions was often insufficiently described. Likewise, adherence was generally poorly described and evaluated differently in the studies, as such an overall summery of adherence have not been made. Studies that did report on adherence recounted adherence ranging from 20% to 98%.

Anabolic steroid in rehabilitation of older patients with hip fracture

The pilot trial (study 2) is to the best of my knowledge the first trial exploring a novel intervention of adding anabolic steroid to physiotherapy and protein-rich nutritional supplement in rehabilitation following hip fracture surgery.

Recruitment

Recruitment in this population of older patients with hip fracture was a challenge (1.8 patients/month) and less than half of the expected based on experiences from a previous RCT conducted at the same unit.[6] However, there were substantial differences in the interventions, as patients in the previous study only committed to a short in-hospital exercise intervention compared to the present study, where patients had to commit to a complex 12-week multimodal intervention. Still, recruitment rates in the present study were comparable to trials with similar interventions.[156–158] For safety reasons relative conservative eligibility criteria were applied in

this trial, since the use of anabolic steroid is novel among older patients with hip fracture, and the eligibility criteria were inspired by other studies using anabolic androgenic steroids in elderly.[156–158] In future trials less restrictive eligibility criteria could be considered. For instance patients with mild cognitive impairments or patients residing at nursing homes, might be able to participate, when they are situated in known surroundings, and receiving support from familiar healthcare workers.[159] In that regard consent by proxy could be considered. Acute illness as a consequence of surgery such as renal impairment and delirium was also cause of ineligibility and might be modified by postponing inclusion 1-2 weeks.

Of the eligible patients 41% were included in the trial. It has previously been established, that recruitment efficacy declines with increasing age of the population, and particularly acute hospitalized geriatric patients tend to be difficult to engage in clinical trials.[87,88,160] Results from the pilot RCT showed that the feeling of being "Overwhelmed and stressed by the situation", was the most frequently reported reason to decline trial participation among the eligible patients. Following a hip fracture the first post-operative days are often characterized by pain, fatigue and severe decline in mobility.[161] Further, qualitative research including a recent systematic review[162–167] have explored patient experiences during this early period after surgery, and findings indicate, that patients feel insecure, vulnerable and in a state of hopelessness after the fracture. Moreover, they express concerns about discharge from the hospital and generally worry about life after the fracture. This is to a great extend in correspondence with findings from the qualitative study (study3), where participants expressed, how they felt distressed and a total lack of energy, at the time they were approached for inclusion. Some participants recalled that they accepted to participate in the trial, as they believed that 'things could not get worse'. This indicates that some participants may have felt despair, but at the same time, that trial participation may have offered hope and an opportunity to get extra care during this time of insecurity.

The acute hospital stay has accelerated considerably within the recent years from median 11 days[6] to median 8 days in the present study, resulting in very limited time for inclusion procedures and outcome assessment. Consequently, patients were approached for inclusion as soon after surgery as possible, which might have impeded recruitment considering the patients state of mind and ability to relate to trial participation at this early timepoint after surgery.

The participants ability to remember and process information might also be reflected in the short baseline interviews (study 3). The participants recounted not having many expectations or specifically not remembering, what they expected prior to enrollment, although the interview

took place 1-2 weeks after enrollment. Additionally, some participants expressed feeling groggy from medicine and not quite being able to comprehend the information provided. This dilemma is also pointed out in a previous study, indicating variations in the patients ability to remember and process information during the acute phase.[162] This draws attention to the schism of patient information having to fulfill authority rules, thus being quite comprehensive and complex in content, but on the other hand also be easy to understand for older adults of whom some might be in crisis.

Acceptability

Our findings suggested excellent adherence and high acceptability of both injections and physiotherapy (including progressive strength training). We anticipated some reluctance towards engaging in a trial applying anabolic steroids in rehabilitation. Positively, findings from study 2 and 3 revealed, that concerns about adverse events related to trial medication was not a major issue for this population, and they generally expressed limited knowledge about anabolic steroid. The patient's narrations about the anabolic steroid indicated, that they were somewhat intrigued about potentially getting anabolic steroids and trusted that benefits outweighed potential harms.

Participants expressed great appreciation of the physiotherapy intervention, and particularly expressed high motivation for, and acceptance of progressive strength training. They appreciated the supervision, as they felt in safe hands and adequately challenged, but also the support and encouragement from the physiotherapist guiding them in their recovery. These findings are supported by two reviews exploring factors important for older adults participation in physical activity[168] and strength training[169] highlighting the importance of social support including verbal encouragement, practical help and individually tailored exercises provided by health professionals. This is further substantiated in a recent review from Beer et al.[167] indicating, that patients with hip fracture feels reliant on support from healthcare professionals and particular physiotherapist to recover successfully from the hip fracture. Participants in the present study valued the session to session feedback on their load progression performing the progressive strength training, which might have served as a motivational factor increasing adherence. Further, a low starting point for the fractured leg strength, might have contributed to relative fast increases in load (32% increase for the fractured leg knee extension within the first 2 weeks). This may have impacted on the participants feeling of success and regain of previous self, which further may have promoted self-efficacy, especially since the success was achieved in the face of challenge, being impaired and experiencing pain.[170] The importance of the therapist-patient

relationship on hip fracture patients motivation for exercise have been described previously,[171] and is further supported by patients describing lack of motivation for non-supervised home exercise.[172] As such, supervision may serve as an essential motivating factor in exercise interventions, and it might be a contributing factor to maintain adherence. Further, supervision may also help ensure adequate quality and intensity of the exercise, all in all resulting in larger effect sizes compared to non-supervised interventions.[68,73] These tendencies were also indicated in study 1, where larger effect sizes were seen for the more comprehensive interventions (12+ supervised sessions) compared to the less comprehensive (0-11 supervised sessions) for the outcomes of mobility, strength and balance, although between group difference were not statistically significant.

Adherence to the nutritional supplement was lower than expected (61%), but nonetheless it was comparable to similar trials.[84,173] Malnutrition and particularly low protein intake is suggested as potential risk factors for sub-optimal recovery in older patients following hip fracture surgery.[43,84,174] A frequently used serum marker of malnutrition is serum albumin, where patients are considered malnourished when serum albumin concentrations are less than 35 g/L.[175] In that regard all participants in the current trial were malnourished at baseline (mean 25.9 g/L (2.8)) (paper 3, eTable 7), but not at follow-up (39.3 g/L (3.3)), and already at the 3 week control the mean values exceeded the malnutrition cut-off. When assessing malnutrition at baseline using MNA-SF questionnaire, no participants were categorized as malnourished, but 5 participants were at risk of malnutrition. Similarly, cut offs for BMI indicating malnutrition proposed by the Global Leadership Initiative on Malnutrition (GLIM), suggested that only 2 participants were malnourished at baseline.[176] The adherence rate and patient narrations reflected, that acceptability of the nutritional supplement predominantly was poor, but due to a feeling of obligation participants made an effort to consume the supplementation. However, efforts were made trying to accommodate the patients, by supplying them with their preferred taste and motivating them to drink one bottle (or as much as possible), if they were unable to consume the two bottles intended. Consideration for future trials, would be an even more individualized and pragmatic approach, as individualized supplementation seems to have more positive effects.[43] For those having sufficient protein intake, additive supplementation will probably not augment the effect of resistance training.[177] As such, a more frequent evaluation of nutritional risk seems relevant to target the intervention, and additionally different types of supplementation might increase acceptability.

The adherence to hospital controls was excellent, although the transportation to and from the hospital for some participants was perceived as time-consuming and strenuous. The high adherence could be explained by the patient's feelings of getting 'something extra', both insight in their recovery by the many measures taken, but also simply the extra attention paid to their wellbeing (study 3). Likewise, the weekly phone calls were greatly appreciated by the participants, and they may have played an important role in the retention of participants. Previous research have indicated the importance of information and support from healthcare professionals in the recovery after hip fracture[167,172,178] and that health professionals encouragement and support have potential to promote the patients feeling of self-efficacy.[170,179] The participants weekly contact with health professionals and the continuous feedback on their recovery might also have been a factor modifying and balancing the participants outcome expectations in a way that made expectations realistic, and thus contributed to the positive perception of trial participation and recovery.[167,170]

Knee-extension strength

In study 2 positive tendencies in favor of the intervention group were seen for the addition of anabolic steroid on the primary outcome of knee-extension strength. Additionally, in the per protocol analysis of patient's adherent to the anabolic steroid, between-group differences in knee extension strength reached the level of significance for the non-fractured leg (p=0.046) in favor of intervention group.

The effect of anabolic steroids on knee extension strength in patients following hip fracture have not previously been investigated, but two studies in other populations facing similar challenges of muscle strength declines have explored the impact of anabolic steroid on knee extension strength. A three armed study by Johansen et al.[81] found no effect of nandrolone alone (♀:100mg, ♂:200mg/week) on knee extension strength (measured by 3RM) after 3 months in middle aged patients undergoing hemodialysis, but a statistical significant effect of progressive resistance training both alone and in combination with nandrolone. However, in the same study also isokinetic knee extension strength was measured and showed no significant effects for either groups receiving nandrolone, progressive resistance training or the combination of the two. Another very small study including 10 male participants with osteoarthritis, who had a total knee arthroplasty found indications of larger increase in isokinetic knee extension strength after 3, 6 and 12 months in patients receiving nandrolone (50mg/bi-weekly/6months) compared to placebo.[180]

In the present study, there seemed to be a tendency of a more pronounced signal of the intervention in the non-fractured leg, which might be explained by less variance or 'noise' induced by trauma and surgery including pain and edema.[33,39] Yet, we did not find indications of pain being a limiting factor during strength-testing, with only two in the intervention group and four in the control group expressing moderate to severe pain (VRS>1) at baseline, and none of the participants reported moderate to severe pain at follow-up (study 2).

Knee extension strength was chosen as the primary outcome, as it is perceived to be a relevant outcome in patients with hip fracture as low knee extension strength is associated with impaired physical function, mobility, falls and mortality,[7,181–184] but also considering the large prevalence of sarcopenia in patients with hip fracture.[52–56] Further, it was a measure applicable in the acute setting allowing us to assess knee extension strength at the bedside. Previous studies has proven good feasibility[6,9,185] and high test-retest reliability (ICC=0.95) of knee extension strength measures with a belt fixated dynamometer in patients with hip fracture.[101] The belt fixated method is preferred over non fixated measures, as it allows for higher values of strength to be measured, because it is independent of the assessors strength.[186] Standard error of measurement (SEM) has been calculated to be 1.0 kg (9.8 N), and the minimum detectable change at the 90% confidence level (MDC_{90}) to be 2.3 kg (20.7 N) for the fractured leg, and corresponding SEM = 1.6 kg (15.7 N) and MDC_{90} = 3.7 kg (36.3 N) for the non-fractured leg.[187] Within group differences measured in Newton in the present study was (INT: fractured 129.9 N, non-fractured 51.8 N and CON: fractured 106.6 N, non-fractured 15.2 N). As such, only the non-fractured leg strength in the control group had a change score that potentially could be due to measurement error and not a real change.

Secondary outcomes

We did not identify significant between-group differences for the secondary performance measures or patient reported outcomes. Handgrip strength was chosen as an outcome that could reflect a general strength increase attributed to the anabolic steroid, as no specific strength exercises was performed for the upper extremities. Although, the intervention group had a slight increase in handgrip strength and the control a decrease, the between group differences did not reach significance. Expectedly, significant positive within-group changes were seen for gait, mobility and fear of falling, but no within-group change were seen for QoL, fatigue, depression, which is in accordance with similar studies of exercise interventions following hip fracture.[138,140] Low testosterone levels were identified for both genders at baseline, with only 1 male and 3 female participants having baseline values within the reference interval for the respective gender.

Expectedly, higher testosterone levels were identified in the intervention group compared to the placebo group at follow-up.

Hip fracture patients have an accelerated loss of BMD following the fracture.[188–190] Compared to matched controls without hip fracture the loss of BMD is 12 times greater for the femoral neck area, and 5 times greater for the total hip area, one year after the fracture.[190] In the present study, we did not reach a significant between group difference in total BMD, but the intervention group showed a significant within group increase in total BMD whereas values decreased for the control group.

Contrary to previous findings indicating effect of anabolic steroids on LBM in patients with hip fracture,[191] we did not find significant between-group differences for measures of LBM in the present study, which could be explained by a short treatment period and a small sample size. Weight loss was seen for both groups and was probably caused by the post-surgery edema and fluid retention at the time of baseline assessment, and it corresponds to the reduction in total LBM. Generally, LBM is reduced following hip fracture with around 3.4%-6.4% two months after surgery.[188,189]

Part of the pilot trial was to assess feasibility and suitability of outcome measures, in order to narrow down which outcomes could be the most suitable to apply in a larger confirmatory trial. Our findings did not give a clear indication of some outcomes being superior to others. The performance measures related to gait and mobility all seemed feasible to perform in this group of better functioning patients, however not all patients with hip fracture would be able to independently perform TUG and 10 MWT before discharge, which favors to keep DEMMI as an outcome in combination with either TUG or 10 MWT. In relation to the PROM's the GDS could be left out, as depression and anxiety were covered in the EQ5D-3L. Further, for the SF36 fatigue subscore, it seems the patients had difficulties distinguishing the 4 questions from each other and needed support from the assessor. A measure of ADL was not included in the present study, but could have been relevant, and is also considered a core outcome measure following hip fracture.[192] However outcome measures should be restricted to a minimum to avoid exhaustion of the participants, and for outcome assessment to be feasible shortly after surgery.

Adverse events

Adverse events related to anabolic steroid was a concern, especially female hirsutism, as few cases were previously reported in a similar study with 1 year treatment of anabolic steroid.[158] In the present study adverse events were equally distributed between the two groups. One female participant reported a slight increase in facial hair growth on the chin, but she frequently shaved

prior to the trial, and she expressed no concerns regarding this matter. Nonetheless, she stopped injections, as she experienced discomfort from increased perspiration. Three cases of increased liver parameters were identified. Two participants (one in each group) had levels above the prespecified safety threshold, and therefore the injections were ceased (parameters normalized within 2 weeks).

Methodological considerations

The broad scope of the systematic review (study 1), introduced statistical heterogeneity in the meta-analyses which contributed to downgrading of the body of evidence. Nonetheless, some heterogeneity was expected, because of the large variance in the target population, interventions and outcome measures in these studies of exercise therapy following hip fracture. Generally, subgroup analyses did not explain the heterogeneity, therefore the subgroup results should also be interpreted with caution.

The fact that adverse events was poorly reported in the individual studies, limits the overall evaluation of the benefit of exercise therapy. Nevertheless, findings from a 2020 systematic review[193] suggested that participating in exercise therapy did not increase the risk of a serious adverse events in a mixed population, where the largest subgroup was older adults. Non-serious adverse events increased by 19%, but were mostly limited to muscle soreness, fatigue and pain. Therefore, exercise therapy could be considered relatively safe and advantages would largely outweigh risks.

The multimodal intervention applied in study 2 could be considered complex, as it included several interacting components, reached across sectors and required new behaviours of those delivering and receiving the intervention.[89] We sought to include various stakeholders throughout the trial. As such physiotherapists from the participating 10 municipalities were involved in the process of designing and describing the physiotherapy intervention. During the course of the trial there was a close correspondence between the PhD student and the municipality-based physiotherapists to clarify any challenges that emerged. Further, in study 3 the patient's perspective was explored, providing valuable information on the participants motivation for engaging in the trial and the acceptability of the intervention, which is considered important factors to clarify before potentially upscaling to a larger confirmatory trial.

The pilot trial was limited by the low inclusion rate, and that target sample size was not reached. Nevertheless, the trial was not intended to make solid conclusions for or against the intervention,

as even with the planned 48 participants, power calculations was only intended to give indications of preliminary effect.

The participants in study 2 had a higher pre-fracture functional level measured by NMS (mean 8.6) and were younger (mean 73.4 years) than the general population of older hip fracture patients admitted from own home (53% having NMS 7-9, mean 81 years).[194] Hence, generalizability of the results are limited to a similar population. Nonetheless, the better functioning hip fracture patients still have considerable deficits in strength and recovery rates. Thus, it has previously been shown, that almost half of better functioning hip fracture patients (72% with NMS 7-9) were classified as probable sarcopenic using cut-points for knee extension strength of the non-fractured leg and hand grip strength.[55] Similarly, in the present study when applying cut points for risk of severe mobility limitations[183] 4 out of 5 male participants had moderate or high risk of severe mobility limitations, and the corresponding proportion of female participants was 13 out of 16 who were in moderate or high risk of severe mobility limitations. When looking at recovery rates, a review by Dyer et al.[13] showed that among the patients independent in mobility pre-fracture, only 40-44 % recovered the independence after 1 year. Similarly, in a recent study by Overgaard et al.[12] patients having a high pre-fracture functional level (NMS>8) who had participated in either 6 or 12 weeks of outpatient physiotherapy including progressive strength training, only 54% had regained pre-fracture level 6 month after the fracture.[12] In the present study positively 81% regained their pre-fracture function, participants had pre-fracture NMS comparable to those in the study by Overgaard[12] but were slightly younger.

Conversely, it could also be argued, that the addition of muscle enhancing medicine in rehabilitation would be relevant for the more impaired and older patients with hip fracture. It might even offer a pharmacological alternative to very impaired patients unable to sufficiently perform exercise therapy (including progressive strength training).[47]

It is considerate a strength, that the deliverance of the trial specific physiotherapy intervention was designed to mimic usual practice in the municipalities, in order to enhance generalizability and ease implementation. Further, it was of immense importance, that progressive strength training was demonstrated to be feasible, with high adherence and high acceptability. Strength training seems vital for patients with hip fracture to increase function and avoid the downward spiral of deconditioning, future falls and subsequent fractures.[47] Especially considering the prevalence of sarcopenia in this population, and the further decline in muscle strength occurring as a consequence of the fracture.[43]

Nutritional supplement is part of standard care during hospitalization, but also in the municipalities there is an increasing focus on nutrition in fragile geriatric patients, as recommended by a national clinical guideline from 2016.[195] As such, some municipalities perform nutritional screening as part of the rehabilitation program for patients with hip fracture, and patients at nutritional risk will be offered dietician intervention. Therefore, an individualized nutritional intervention following hip fracture should be implementable during the entire course of the rehabilitation.

Findings from the interview study was mainly positive with great acceptance of the multicomponent intervention. Social desirability bias, where responses are adjusted to what participants believe is socially acceptable or pleases the interviewer,[196] could be a limiting issue. However, we tried to address this matter, by the follow-up interviews being conducted by an interviewer, that the participants were not familiar with, and who was not otherwise involved in the trial. Further, we emphasized that all opinions, both negative and positive, were valued. It adds to the credibility of our findings that many of the emerging categories where supported by corresponding findings in other studies exploring older adults' recovery from hip fracture.

Conclusion

In conclusion, our findings indicate that exercise therapy has potential to reduce the negative impact of a hip fracture, as small to moderate effect sizes were identified for several patient important outcomes. As such, we found low certainty evidence for a moderate effect of exercise therapy on mobility in older patients following hip fracture, which was sustained at long-term follow-up. Moreover, low certainty evidence was found for small to moderate effects on ADL, lower limb muscle strength, balance, endurance and falls at short-term follow-up; and at long-term follow-up for ADL, HRQoL and balance. Subgroup analyses suggested that strength training improves strength, ADL-training improves ADL, and functional training and strength training improves mobility and balance. These findings may help guide and qualify future exercise therapy provided to older patients during their cross-continuum physical rehabilitation.

Findings of the pilot RCT revealed difficulties of early recruitment, during acute hospitalization following a hip fracture to a multimodal cross-continuum trial, reducing the overall feasibility of the trial. On the contrary findings suggested high acceptability of the intervention, with excellent adherence for both anabolic steroid and physiotherapy. Further, high acceptability was established by findings from the embedded qualitative study indicating, that the participants found the possibility of receiving anabolic steroids intriguing. Further, the participants highly appreciated trial participation because of the close contact and support from health professionals, and they valued the supervised progressive strength training, which they perceived as a key component of recovery. Although the trial was inconclusive due to the small sample size, the addition of anabolic steroid indicated promising tendencies. The findings provide important knowledge on feasibility and acceptability, which can help inform future trials and draws awareness to the difficulties and complexity of performing interventional studies in this population of older patients with hip fracture. Additionally, findings suggest a potential impact of professional guidance and support in the promotion of motivation and self-efficacy in this population of older hip fracture patients.

Perspectives

Based on the findings of this thesis, and the existing knowledge within this field, suggestions for post-operative exercise therapy for older persons following hip fracture should consist of a combination of several exercise modalities each targeting different relevant outcomes. Due to the highly accelerated acute hospital stay (at least in a Danish context), early inpatient exercise therapy should primarily focus on early mobilization[187] and functional exercise aiming at recovering basic mobility.[197] In addition, ADL training should be provided to enhance independence in daily activities, preparing patients for the transition to own home, and preferably be continued during the first weeks at home. Further, exercise therapy in the subacute phase could be compromised of functional training (including balance training) and strength training. Even though trials on the effect of aerobic exercise in patients following hip fracture are few, a suggestion would be to integrate aerobic exercise, as it seem to have a positive effect on age-related insulin resistance and thereby the ability to enhance muscle protein synthesis,[198] but this area needs further investigation. Exercise therapy should preferably be supervised to maintain intensity, motivation and adherence. Further, supervision and support from health professionals might play a role in promoting self-efficacy. However, the effect of motivational strategies within hip fracture rehabilitation needs further investigation. In addition, although the effect of exercise therapy for hip fracture patients have been extensively studied, more high-quality trials seems relevant to establish the most effective combination of exercise modalities, intensity and timing. Further, 'one size may not fit all' and future research could look into how patient characteristics might influence on the effect of exercise therapy. Moreover, future research should pay great attention to sufficient and transparent reporting, to increase evaluation of quality and certainty in the evidence.

Despite promising effects of exercise therapy, a multimodal approach including muscle enhancing medicine has been proposed to bring a larger proportion of patients back to pre-fracture function. In that regard, our findings of high acceptability of anabolic steroid in addition to physiotherapy and nutritional supplement are of great relevance for future research. The positive tendencies of the effect of exercise therapy on knee extension muscle strength, provides incitement to conduct a larger confirmatory trial establishing effect, safety and cost-effectiveness. However, when upscaling to a confirmatory trial, special attention should be paid to increase recruitment, and a suggestion would be to establish contact to the patient during acute hospitalization, but postpone final inclusion to after the patients is settled at home (2nd or 3rd

week after surgery). To meet target sample size within reasonable time a multicenter study would be relevant. Additionally, the hospital controls every 3rd week (including administration of trial medication) could take place at the patient's home, to eliminate the barrier of attending controls at the hospital for the more disabled patients.

A clinical practice guideline for physical therapy management of hip fracture patients has just been published[187], and across the entire continuum of care the guideline suggest strong recommendations for structured exercise including progressive strength training, balance training, weightbearing, and functional training, which is largely consistent with findings from study 1. As strength training seems to be a key ingredient not only in hip fracture rehabilitation, but also in the treatment of sarcopenia and is generally considered a means of maintaining good health in old age (WHO),[199] our finding of high acceptability of progressive resistance training among older adults with hip fracture is of immense importance. Finally, it seems important to emphasize, that although a targeted intensive multicomponent intervention during the first months after hip fracture seems crucial, physical activity and exercise should be life-long to sustain physical function and postpone deconditioning for as long as possible as recommended by WHO.[199] Therefore our finding, that the participants in the pilot trial wished to continue exercising or had already initiated exercise is of great significance, and indicates that trial participation might have promoted self-efficacy which needs further focus in future research.

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Appendix

Paper 1

Paper 2

Paper 3

Paper 4

Paper 1

Exercise therapy is effective at improving short- and long-term mobility, ADL and balance in older patients following hip fracture: a systematic review and meta-analysis.

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Exercise therapy is effective at improving short- and long-term mobility, ADL and balance in older patients following hip fracture: a systematic review and meta-analysis.

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Abstract

Background: A systematic review and meta-analysis was performed to evaluate the short- and long-term effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture, and secondly, whether the effect was modified by trial level characteristics such as intervention modality, duration and initiation timepoint.

Methods: Medline, CENTRAL, Embase, CINAHL and PEDro was searched up-to November 2020. Eligibility criteria was randomized controlled trials investigating the effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture, initiated from time of surgery up-to 1-year.

Results: Forty-nine studies involving 3905 participants showed a small to moderate effect of exercise therapy at short term (end of intervention) on mobility (Standardized mean difference, SMD 0.49, 95%CI 0.22-0.76); Activities of Daily Living (ADL) (SMD 0.31, 95%CI 0.16-0.46); lower limb muscle strength (SMD 0.36, 95%CI 0.13-0.60); balance (SMD 0.34, 95%CI 0.14-0.54). At long term (closest to 1-year), small to moderate effects were found for mobility (SMD 0.74, 95%CI 0.15-1.34); ADL (SMD 0.42, 95%CI 0.23-0.61); balance (SMD 0.50, 95%CI 0.07-0.94) and Health related Quality of Life (HRQoL) (SMD 0.31, 95%CI 0.03-0.59). Certainty of evidence was evaluated using GRADE ranging from moderate to very low, due to study limitation and inconsistency.

Conclusion:

We found low certainty of evidence for a moderate effect of exercise therapy on mobility in older patients following hip fracture at end-of-treatment and follow-up. Further, low evidence

was found for small to moderate short-term effect on ADL, lower limb muscle strength and balance.

Trial registration: CRD42020161131

Keywords: Rehabilitation, Exercise, Physical therapy, Occupational therapy, Physical function

Introduction

Sustaining a hip fracture has large consequences for older patients, with loss of muscle strength and physical function leading to loss of independence, increased risk of secondary fractures and death (1–6). Regaining independent mobility after a hip fracture is therefore essential and is considered the primary goal of hip fracture rehabilitation. Previous research shows that up to 50% of patients with hip fracture do not regain prefracture function one year post surgery (3,7).

Rehabilitation interventions consisting of physiotherapy and occupational therapy are often provided concurrently following hip fracture, but with large variations in time of initiation, content, duration, and intensity of the interventions provided. A Cochrane review from 2011 by Handoll et al. showed insufficient evidence of the effect of mobilization strategies, but indicated, that increasing mobility after hip fracture was possible, though the optimal method remained unclear (8). Accordingly, previous systematic reviews (9,10) evaluating the effects of rehabilitation interventions and occupational therapy on improving physical function and independence, were inconclusive, although positive trends were shown. The reviews were limited by few trials and large heterogeneity. In 2016 Diong et al. showed a small significant effect of structured exercise on mobility in a systematic review and meta-analysis (11). As such, exercise therapy following hip fracture might have the potential to reduce loss of mobility and increase independence. A large number of new trials have been published within the last years, which calls for an update on the effects of exercise therapy in older patients following hip fracture.

This systematic review aimed to evaluate the short- and long-term effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture from the time of surgery until 1 year after surgery, and secondly, to determine if the effect of

exercise therapy was modified by trial level characteristics such as intervention modality, duration and initiation timepoint.

Research questions:

1. *What is the effect of exercise therapy on physical function, independence and wellbeing in older patients following hip fracture, when the intervention is initiated within the 1st year after surgery?*
2. *Is the effect of exercise therapy modified by the following trial level characteristics: Initiation point of intervention, setting, duration of intervention, intervention modality, comparator being active/passive, comprehensiveness of interventions and risk of bias?*

Methods

This systematic review and meta-analysis was conducted according to the Cochrane Handbook (12) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). The study is pre-registered with the International Prospective Register of Systematic reviews (PROSPERO) in February 2020 (CRD42020161131).

Changes to pre-registration

Due to the large heterogeneity of the physiotherapy and occupational therapy interventions and an extensive amount of information, this review report focuses on the effect of exercise therapy. We will subsequently publish a review report that focuses on the effect of motivational and educational interventions led by physiotherapists and occupational therapists.

Eligibility criteria.

We included randomized controlled trials (RCT) (individual and cluster) and quasi-randomized controlled trials investigating the effect of exercise therapy interventions on physical function and wellbeing and initiated within the first year after surgery. We defined exercise therapy as exercise interventions, that were (or could be) led by physiotherapists or occupational therapists. Interventions involving electrical stimulation was included within this definition in the present study. The intervention should contain an interaction between physiotherapists or occupational therapists and the patient, and as such a written instruction was not considered an exercise therapy intervention. Further, trials were included if nutrition or vitamin supplement was offered as a co-intervention. On the contrary, studies of multimodal or multidisciplinary interventions including medical or nursing interventions were not included. Interventions could be compared to usual care, a different intervention, or no intervention. Inclusion was restricted to participants who had undergone surgery for a hip fracture, and with a mean age of the study population equal to or above 60 years. Only papers in English, Danish, Swedish, Norwegian and German were eligible.

Data sources and search strategy

The following electronic bibliographic databases was searched up to 16th November 2020: Medline (via Pubmed), Cochrane Central register of Controlled Trials (CENTRAL), Embase (via Ovid), CINAHL (via EBSCO) and PEDro. Reference lists of included studies and relevant systematic reviews were searched manually. The search strategy included MeSH terms and text words relating to the population and intervention. As such the search was a combination of synonyms for 'hip fracture' AND 'exercise'. In order to restrict the search to randomized controlled trials (RCTs) we applied the "Cochrane Highly Sensitive Search

Strategies for identifying randomized controlled trials" (12). The only filter applied was publication after 1990, due to expected change in rehabilitation. The search strategies were developed with assistance from a health science librarian. The search strategy performed in Medline are shown in supplementary eMethods 1. ClinicalTrials.gov was searched for ongoing and recently completed trials.

Study selection

After removal of duplicates three reviewers (SH, MTK and AR) independently screened titles and abstracts according to the eligibility criteria. Discrepancies between reviewers were discussed until consensus was reached. Studies passing the initial screening were subject to full-text examination by two of the above-mentioned reviewers, in case of discrepancies, the third reviewer were consulted, and the case discussed until consensus was reached.

Outcome variables

The chosen outcomes were inspired by core health outcomes in clinical hip fracture trials (14) as advocated by COMET (15) and qualitative studies exploring patient perspectives of important factors following hip fracture surgery (16–18).

Prioritized list of outcome domains:

1) Mobility

   Composite mobility measures (scales seeking to measure different aspects of mobility) had the highest priority. Secondly, measures of walking ability (e.g. Gait speed). Objective measures ranked higher than self-reported measures.

2) Activities of daily living (ADL)

   Objective measures od ADL ranked higher than self-reported measures.

3) Health Related Quality of Life measures (HRQoL).

If a total score was not provided, the most general subscore was used.

4) Muscle strength in the lower limb

   Direct measures (e.g. specific muscle strength test) before surrogate measures (e.g. Chair Stand Test). If several measures of 'direct' lower limp muscle strength, priority were as follows: Knee-extension, leg-press, hip abduction, hip extension, calf (plantar flexion), knee flexion. The prioritization was based on anti-gravity muscles first. If knee-extension was measured on both affected/unaffected side, affected side were prioritized.

5) Balance

   Direct (balance platform) before indirect, and composite measures of balance before a single measure.

6) Endurance

   Direct measures (e.g. VO2max) before indirect (6 min walk).

7) Physical activity

   Upright time, time walking, sedentary time were prioritized first. Secondly, number of steps before self-reported measures.

8) Fear of falling

9) Falls (only if specified as outcome)

If more than one outcome measure was reported within one outcome domain, the above list of priorities was used to determine which outcome data to extract on. If more than one measure within the same prioritized domain were reported, the one presented first in the methods section in the original article, was extracted. If there were several follow-up times for the outcome, the two timepoints that were synthetized were 1. Short-term (end of intervention) 2. Long-term (closest to 1 year).

Data collection

A data extraction sheet was developed in Excel. One reviewer extracted trial level characteristics which was verified by a second reviewer. Data on effect sizes was retrieved by two reviewers independently. The following data was extracted: Author, year of publication, country, number of participants, age, gender, study period, primary intervention modality, description of intervention, primary setting, initiation timepoint following surgery, duration of intervention, providers of intervention, supervision, characteristic of comparator, outcomes, follow-up timepoint, adherence, adverse events, and trial registration. Studies including two relevant interventions, were divided into two studies (e.g. strength training vs control and aerobic training vs control), and number of participants in control group was halved to avoid double counting of controls.

Assessment of risk of bias

Risk of bias for the effect estimates in the individual studies were assessed using Cochrane Risk of Bias Tool 2 (ROB2) (19), covering: 1. Bias arising from the randomization process; 2. Bias due to deviations from intended interventions (effect of assignment to intervention); 3. Bias due to missing outcome data; 4. Bias in measurement of the outcome; 5. Bias in selection of the reported result. The ROB2 assessment is specific to the effect estimate for a particular result (19). If a trial reported on both an objective (performance) measure and self-reported measure, two assessments were made, and therefore two overall risk of bias scores are presented. If the trials contributed to the review with more than one objective or patient reported result, the result assessed was chosen according to our prioritized list of outcomes, and the assessment applied to the other objective/patient reported outcomes in the trial (12). Further, if a trial had more than one follow-up time-point, the first one (end of intervention)

was chosen for the ROB2 assessment. The assessment was performed independently by at least two reviewers, (SH, MTK and AR). Disagreements were resolved by consensus.

Assessment of certainty in the body of evidence

Assessment of certainty in the body of evidence was conducted using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) (20). The assessment covers study limitation, inconsistency, indirectness, imprecision, and publications bias.

Summery measures and data synthesis

For each outcome, number of participants, change score and corresponding standard deviation (SD) were extracted for intervention and control group. If SD was not presented in the original article, it was estimated from the standard error (SE), 95% Confidence Interval (95%CI), p-value or other methods as recommended by the Cochrane Handbook (12). In cases where only SD on baseline and follow-up scores were available a correlation of 0.7 was assumed between baseline and follow-up scores in order to estimate SD of the change score (21). In cases where data from the individual studies were only presented in figures, SD was measured from figures.

The effect of the individual studies was pooled using a random effects model (restricted maximum likelihood method, REML) as heterogeneity was expected due to differences in participants, interventions and outcome. The pooled effect size was expressed as standardized mean differences (SMD) by dividing the mean group difference with the pooled standard deviation (SD). To adjust for overestimating effect size in small studies, a correction factor was applied to convert the estimate to 'Hedges g'. Effect sizes were interpreted as original proposed by Cohen; SMD equal to 0.2 was considered small, 0.5 as moderate and 0.8 as

large. Heterogeneity was examined as between study variance (tau^2) and as I^2-statistics measuring the percentage of variation attributable to inconsistency. The possibility of small sample bias was investigated using Eggers test and funnel plots for outcomes with sufficient studies (more than 10), the plots were interpreted using visual inspection.

Subgroup analysis was performed to investigate the impact of the following trial characteristic: Initiation of intervention (0-2 weeks, 3-16 weeks, 17+ weeks); Primary setting (acute hospital, 24 hour rehabilitation, home rehabilitation, outpatient rehabilitation); Duration of intervention (very short (0-2 weeks), short (3-12 weeks), moderate (13-25 weeks), long (26+ weeks)); Intervention modality (ADL training, aerobic exercise, bed exercises, combined exercises (combination of strength training, aerobic training, and functional exercises), electrical stimulation, functional exercise (including balance training), strength training, breathing exercise) (see supplementary eMethods 2 for elaboration); Control intervention (active, passive); Comprehensiveness of intervention (0-11 supervised sessions, 12+ supervised sessions), Risk of bias (low, some concern, high). Subgroup analysis for an outcome domain was performed only if more than 15 studies reported results within the outcome domain, and the analysis method was the same as described above only stratified for subgroup. The analyses were performed using STATA version 16.

Results

Study selection and characteristics

The literature search identified 6093 hits. After removal of duplicates, 3802 were left for title and abstract screening. Full-text screening was conducted for 95 studies and 49 studies (22,23,32–41,24,42–51,25,52–61,26,62–70,27–31) (54 study comparisons) were included in this review. Five of the 49 studies (24,26,40,56,63) did not provide data relevant for pooling in the quantitative synthesis, leaving 44 studies (22,23,35,36,38,39,41–46,25,47–

55,57,27,58–62,64–68,28,69–71,29–31,33,34) for the meta-analysis including 49 comparisons. Figure 1 illustrates the study selection process.

Study characteristics

The 49 studies included a total of 3905 participants. Demographics and study characteristics are presented in supplementary eTable 1. Sample size in the included studies ranged from 20 to 304. The included studies were carried out in 20 countries across 4 continents (Europe n=23, North America n=11, Asia n=5, Australia n=9). The average age of the study participants was 80.6 years (range 73-85 years). The proportion of women in the included studies was on average 79,6% (range 59.5-100%). Nine studies were carried out in the acute care setting, 12 during 24-hour rehabilitation, 21 as home rehabilitation and 7 in an outpatient setting. The primary intervention modality was: Strength training (n=14), functional training (n=15), electrical stimulation (n=3), ADL training (n=3), aerobic training (n=3), combined exercises (n=11), bed exercises (n=1), and breathing exercises (n=1).

Risk of bias in the included studies

Using ROB2 only effect estimates in one study was evaluated as having low risk of bias (41) for the objective outcome measures, 27 were categorized as having 'some concerns', and 20 at high risk of bias. For the patient reported outcomes no effect estimates were rated as low risk of bias, 18 were rated 'some concerns', and 15 at 'high' risk of bias. See supplementary eTable 2 for an overview of the ROB2 assessment.

Certainty of the evidence

Assessment of certainty in the body of evidence using GRADE is presented in the 'Summary of findings' (table 1).

Mobility

Mobility was reported in 33 studies including 2754 participants. Participating in exercise therapy showed a moderate positive effect on mobility at short-term follow-up of SMD 0.49 (95%CI 0.22 to 0.76), but with considerable heterogeneity I^2=90.94% (figure 2+3). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

In subgroup analysis (figure 4) 'Modality of intervention' showed statistically significant between group effect (p=0.04), with functional exercises indicating a statistically significant moderate effect on mobility (SMD 0.58, 95%CI 0.22 to 0.94, 1224 participants, 14 studies, p=0.002, I^2=87.22), and strength training with an insignificant but large effect on mobility (SMD 0.74, 95%CI -0.05 to 1.52, 751 participants; 11 studies; p=0.065, I^2=95.48). Further, subgroup analysis indicated statistically significant between group effects for Risk of bias (p=0.003) with studies categorized as "Some concern" showing a significant effect (SMD 0.70, 95%CI 0.29 to 1.10, 1635 participants, 24 studies, p=0.001, I^2=93.07). No other subgroup analysis showed statistically significant between group differences.

For the outcome 'Mobility', 15 studies (1185 participants) contributed with data on long-term follow-up (the timepoint closest to 1 year). Analysis showed a large statistically significant effect of SMD 0.74 (95%CI 0.15 to 1.34) but with considerable heterogeneity of I^2=95.47% (figure 2 and supplementary eFigure 1).

Two studies (48,61) reported very large effect sizes, and therefore an additional sensitivity analysis were performed excluding those two studies. The result did not change markedly, and as such considered robust.

ADL

ADL was reported in 21 studies (2066 participants) at short-term, and the meta-analysis showed an overall significant effect of exercise therapy SMD 0.31 (95%CI 0.16 to 0.46) on ADL, with substantial heterogeneity I^2=60.78% (Figure 2 and supplementary eFigure 2). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Stratified analyses for ADL are presented in supplementary eFigure 3. The effect of the interventions appeared to be modified by: Primary setting (p=0.01), with largest effect size for acute hospital (SMD 0.62, 95%CI 0.38 to 0.85, participants 301, studies 3, p<0.001, I^2=64.65); Duration of intervention (p=0.01), with largest effect for very short interventions 0-2 weeks (SMD 0.66, 95%CI 0.38 to 0.94, 260 participants, 3 studies, p<0.001, I^2=19.25); Modality of intervention (p<0.001), with largest effect for ADL training (SMD 0.59, 95%CI 0.31 to 0.87, 253 participants, p<0.001, I^2=14.63) and breathing exercises (SMD 0.62, 95%CI 0.17 to 1.08, 79 participants, 1 study, p=0.007); Comprehensiveness of intervention (p=0.01) with largest effect for less comprehensive intervention of 0-12 supervised sessions (SMD 0.53, 95%CI 0.34 to 0.73, 602 participants, 6 studies, p<0.001, I^2=22.50); Risk of bias (p=0.01), largest effect for studies classified as “some concern” (SMD 0.53, 95%CI 0.34 to 0.73, 1343 participants, 14studies, p<0.001, I^2=52.10).

Long-term effect of exercise therapy on ADL was investigated in 12 studies (1102 participants). A statistically significant moderate effect size of 0.42 (95%CI 0.23 to 0.61), with moderate heterogeneity of 47.88% was found. See figure 2 and supplementary eFigure 4.

HRQoL

Health related quality of life was investigated in 20 studies with 1537 participants at short-term follow-up. Meta-analysis showed no statistically significant effect of exercise therapy on HRQoL in patients recovering from a hip fracture SMD 0.13 (95%CI -0.05 to 0.30) with substantial heterogeneity I^2=62.16% (Figure 2 and supplementary eFigure 5). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Stratified analysis showed that none of the strata modified the effect of exercise therapy on HRQoL (supplementary eFigure 6).

Long-term effects were investigated pooling data from 13 studies (669 participants). A statistically significant small effect SMD 0.31 (95%CI 0.03 to 0.59) was identified with substantial heterogeneity of I^2=64.83%. See figure 2 and supplementary eFigure 7.

Lower limb muscle strength

Muscle strength was reported in 25 studies and 2045 participants provided data for investigating the effect of exercise therapy on lower limb muscle strength at short-term. A statistically significant overall effect SMD 0.36 (95%CI 0.13 to 0.60) with considerable heterogeneity I^2=83.48% was found (figure 2 and supplementary eFigure 8). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

In subgroup analysis (supplementary eFigure 9) 'Risk of bias' showed statistically significant between groups effect (p<0.001), with 'some concerns' having the largest effect size (SMD 0.54, 95%CI 0.24 to 0.85, 1405 participants, 19 studies, p=0.001, I^2=84.78). Intervention modality showed effect modification (p=0.07) with a statistically significant effect of strength training (SMD 0.72, 95%CI 0.27 to 1.18, 789 participants, 12 studies, p=0.002, I^2=87.37).

12 studies (960 participants) were pooled to investigate the long-term effect of exercise therapy on lower limb muscle strength, and a statistical non-significant moderate effect of SMD 0.45 (95%CI -0.12 to 1.02) was identified, with considerable heterogeneity of I^2=93.53% (figure 2 and supplementary eFigure 10).

Balance

The meta-analysis of the effect of exercise therapy on balance was informed by 20 studies including 1846 participants at short-term. A small but statistically significant effect of SMD 0.34 (95%CI 0.14 to 0.54), with substantial heterogeneity I^2=74.92% (figure 2 and supplementary eFigure 11). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Stratified analysis showed that the effect was modified by setting, duration of intervention and modality (functional exercise and strength training having statistically significant moderate effect sizes of SMD 0.45 (95%CI 0.01 to 0.89, 754 participants, 9 studies, p=0.047, I^2=84.76) and SMD 0.57 (95%CI 0.26 to 0.87, 418 participants, 5 studies, p<0.001, I^2=46.78) respectively). See supplementary eFigure 12.

In long-term analysis 10 studies (878 participants) were included and showed a statistically significant moderate effect of SMD 0.50 (95%CI 0.07 to 0.94), with considerable heterogeneity of I^2=87.45% (figure 2 and supplementary eFigure 13).

Endurance

The meta-analysis pooling data from 7 studies (608 participants) showed statistically significant moderate effect of exercise therapy on endurance SMD 0.38 (95%CI 0.04 to 0.72) at short-term, heterogeneity was substantial I^2=67.70% (figure 2 and supplementary eFigure

14). The body of evidence was judged as low certainty with downgrading due to study limitation and inconsistency.

Physical activity

Five studies informed the meta-analysis on the effect of exercise therapy on physical activity (504 participants) and showed a statistical non-significant small effect SMD 0.20 (95%CI -0.23 to 0.63), with considerable heterogeneity I^2=88.63 (figure 2 and supplementary eFigure 15). The body of evidence was judged as very low certainty with downgrading due to study limitations, inconsistency and imprecision.

Falls

Two studies (323 participants) reported on numbers of falls as a predefined outcome at short-term follow-up. The pooled SMD was 0.38 (95%CI 0.16 to 0.60), I^2=0.0% for the effect of exercise therapy on falls (figure 2 and supplementary eFigure 16). The body of evidence was judged as low certainty with downgrading due to study limitations and imprecision.

Fear of falling

The meta-analysis of the effect of exercise therapy on fear of falling was informed by 5 studies (406 participants) and showed no effect SMD 0.08 (95%CI -0.12 to 0.28), heterogeneity I^2=0.0% (supplementary eFigure 17). The body of evidence was judged as moderate certainty with downgrading due to study limitations.

Small sample bias

Overall funnel plots did not indicate signs of small sample bias, nor did Eggers test. Funnel plots for mobility, ADL, HRQol, muscle strength and balance are presented in supplementary eFigure 18-22.

Discussion

This systematic review showed low certainty evidence for a small to moderate effect of exercise therapy at short-term follow-up on mobility, ADL, lower limb muscle strength, balance, endurance and falls but not for HRQoL, physical activity and fear of falling. At long term follow-up the effect of exercise therapy was sustained for mobility, ADL, balance, and falls, while a small statistically significant effect was found for HRQoL. On the contrary no statistically significant long-term effects were identified for muscle strength, endurance, physical activity and fear of falling.

Subgroup analysis on short-term outcomes provided indications of which intervention modalities should be preferred. As such, it seemed that strength training improves strength, ADL-training improves ADL and both functional training and strength training improves mobility and balance. The meta-analysis presented with high heterogeneity, why results should be interpreted with caution.

Findings in context of other evidence

Exercise therapy proved a statistically significant moderate effect on overall mobility following hip fracture and importantly, the effect was maintained at long-term follow-up. These positive findings are supported by recent systematic reviews; Diong et al. in 2016 (11) showed small to moderate effect of structured exercise on mobility, and Beckmann et al. in 2020 (72) showed in-significant moderate effect of exercise started within the first three

months after hip fracture. Intervention modality appeared to modify the effect, and as such it seemed that functional exercise and to some extent strength training had the greatest impact on mobility. Two previous reviews by Lee et al. evaluated the effect of strength training (73) and balance training (74) following hip fracture and in accordance with our finding's strength training showed moderate effect on mobility, lower limb muscle strength and balance, and balance training improved overall physical functioning.

The small to moderate statistical significant effect of exercise therapy on ADL at both short- and long-term follow-up, substantiates previous findings from small meta-analysis (10,73,75). The effect appeared to be modified by setting, duration, comprehensiveness and intervention modality. As such, it seemed that a very short intervention (0-2 weeks) during acute hospitalization, a less comprehensive intervention (0-11 supervised sessions) and intervention modality of ADL training could be efficient in improving ADL after hip fracture in older patients. The largest deficits in ADL are seen during acute care (76,77), and therefore patients would probably have the largest potential for a positive gain by an intensified and focused intervention during this time period. Further, some measurement scales e.g. Barthel Index shows sufficient good scale width during inpatient care (76), but signs of ceiling effect for the better functioning patients when applied for measurement of ADL after the patient have returned to community (77,78).

No statistically significant effect of exercise therapy was identified for HRQoL at short-term follow-up but at long-term a small statistically significant effect was found. Previous reviews of exercise interventions correspondingly showed no significant effect on HRQoL (75,79). As such, it seems as HRQoL is influenced by many factors, which exercise interventions

alone are not able to improve on short-term. However, our findings might indicate a delayed effect, as improvement was found at the long-term.

Across the outcomes of mobility, muscle strength and to some extent balance, there seemed to be tendencies of larger effect sizes for interventions in outpatient setting concurrent with the more comprehensive interventions (12+ supervised sessions) showing larger effect sizes than the less comprehensive (0-12 supervised). Thus, number of supervised sessions seems to be an important factor which might lead to higher intensity of the provided exercise intervention. Subgroup analysis dividing comparator in to 'active' or 'passive' was conducted, since we hypothesized, that the effect of the intervention would be higher for comparisons where the control group was passive. Surprisingly, subgroup analysis showed that it was not the case. This could indicate problems with the classification. For some cases the control intervention was not clearly passive or active, and a subjective decision was made. Insufficient description of control intervention could also have affected the validity of the classification.

Risk of bias

Effect estimates in all but one study was categorized as having 'some concerns' or at 'high' risk of bias. In general, there were concerns across all 5 domains of the ROB2 tool. Domain 2 'bias due to deviations from intended intervention' had largest amount of 'high' risk of bias, primarily due to large non-adherence, and issues with patients seeking additional treatment/training. Domain 5 'Bias in selection of reported outcomes' presented with the largest number of 'some concerns' primarily due to lack of a pre-specified analysis plan (trial protocol or statistical analysis plan).

In subgroup analysis across all outcomes, studies with outcomes assessed as having 'some concerns' appeared to be the category with the largest effect sizes compared to studies with outcomes assessed as having 'high' risk of bias. Therefore, we are less concerned with risk of bias having a large impact on the effect size.

Adherence

Adherence to intervention was generally very poorly described and calculated differently. Therefore, no overall summery of adherence could be made, but in general adherence to interventions ranged from 20% to 98%. Equally the intensity of intervention was insufficiently described and therefore, lack of effect could be due to both low adherence and suboptimal training.

Strength and limitations

This systematic review including 49 studies is to our knowledge the largest systematic review of the effect of exercise therapy following hip fracture. The review provides an up-to-date quantitative synthetizes of the effect of exercise therapy, and adds to the existing body of evidence, by providing an extensive overview of available data at both short- and long-term follow-up on 9 outcomes of high relevance for patients and clinicians. Consequently, the broad scope, induced statistical heterogeneity which contributed to downgrading of the body of evidence. However, trials on exercise therapy provided to patients following hip fracture are different in nature, and some heterogeneity would be expected due to differences in the target population, interventions and outcome measures. The subgroup analyses did generally not explain the large heterogeneity, and as such subgroup results should be interpreted with caution.

An additional strength of this study includes the comprehensive search, and that data extraction and assessment of methodical quality was performed by at least two independent reviewers, factors that have contributed to accuracy of the review and analysis.

The secondary aim of this study was to investigate if trial level characteristics modified the overall effect of exercise therapy, and we have therefor included several subgroup analyses, which might imply a risk of spurious findings. We do however feel that the subgroup analyses, are justified and relevant, as the organization of hip fracture rehabilitation varies a lot from country to country. Thus, some countries have very short admission to acute hospital followed by a long rehabilitation stay; others have longer acute hospital stays followed by outpatient rehabilitation. So even if some subgroups might be overlapping, we believe the subgroup analyses are of relevance for clinicians.

Another limitation of the review is poorly reported adverse events in the individual studies, which limits the evaluation of the overall benefit of the intervention. Nonetheless, a recent systematic review by Niemeijer et al. (80) investigated the risk of adverse events of exercise therapy in a mixed population (the largest subgroup being older adults), and showed that participating in an exercise intervention did not increase the risk of a serious adverse events. Non-serious adverse events increased by 19% and were often limited to fatigue, pain and muscle soreness. Thus, exercise therapy is recommended as a relatively safe intervention.

Conclusion

We found low certainty evidence for a moderate effect of exercise therapy on mobility in older patients following hip fracture, and the effect was maintained at long-term follow-up. Further, low certainty evidence was found for a small to moderate effect on ADL, lower limb muscle strength, balance and endurance and falls at short-term follow-up. The effect was sustained at long-term for ADL, balance and falls. Further, strength training seems to improve strength, ADL-training improves ADL, and functional training and strength improves mobility and balance. The findings may help qualify and standardize rehabilitation offered to older patients with hip fracture during their cross-continuum rehabilitation.

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Contributors

All authors (SH, AR, TB, CJ, MTK) were involved in conceptualizing the study. SH performed literature searches. SH, AR and MTK conducted study selection, data extraction and study quality assessment. CJ provided methodological insight and guidance throughout the process and conducted the meta-analysis. SH drafted the manuscript. All authors critically revised the manuscript and contributed to the final version of the manuscript.

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Conflicts of interest

TB has received speaker's honoraria for talks or expert testimony on the efficacy of exercise therapy to enhance recovery after surgery at meetings or symposia held by biomedical companies (Zimmer Biomet and Novartis). He has also received fees for writing textbook chapters (Munksgaard) and for organising post-graduate education, such as post-graduate courses in clinical exercise physiology or PhD courses on clinical research methodology. He is an exercise physiologist and physical therapist and may have a cognitive exercise bias.

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Captions for table and figures

Table 1: Summary of findings, short term.

Figure 1: Study flow diagram

Figure 2: Forest plots for the effect of exercise therapy on selected outcomes at short- and long-term follow-up after hip fracture.

Figure 3: Forest plot of the effect of exercise therapy on mobility at short-term.

Figure 4: Subgroup analysis of the effect of exercise therapy on mobility.

Table 1: Summary of findings, short term.

Outcomes	SMD (95%CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Exercise intervention			
Mobility	ES = 0.49 (0.22 to 0.76)	2754 (33 studies)	++00 [a,b] Low	Risk of bias: Low 1, Some 24, High 13 Large inconsistency, I^2 = 90.94%
Activity of daily living	ES = 0.31 (0.16 to 0.46)	2066 (21 studies)	++00 [a,b] Low	Risk of bias: Some 14, High 7 Large inconsistency, I^2 = 60.78%
Health Related Quality of life	ES = 0.13 (-0.05 to 0.30)	1537 (20 studies)	++00 [a,b] Low	Risk of bias: Some 13, High 10 Large inconsistency, I^2 = 62.16%
Lower limb muscle strength	ES = 0.36 (0.13 to 0.60)	2045 (25 studies)	++00 [a,b] Low	Risk of bias: Low 1, Some 18, High 10 Large inconsistency, I^2 = 83.48%
Balance	ES = 0.34 (0.14 to 0.54)	1846 (20 studies)	++00 [a,b] Low	Risk of bias: Low 1, Some 15, High 6 Large inconsistency, I^2 = 74.92%
Endurance	ES = 0.38 (0.04 to 0.72)	608 (7 studies)	++00 [a,b] Low	Risk of bias: Low 1, Some 4, High 3 Large inconsistency, I^2 = 67.70%

Physical activity	ES = 0.20 (-0.23 to 0.63)	504 (4 studies)	+000 [a,b,c] Very low	Risk of bias: Some 1, High 4 Large inconsistency, I^2 = 88.63% CI covered both no effect and moderate benefit
Falls	ES = 0.38 (0.16 to 0.60)	323 (2 studies)	++00[a,c] Low	Risk of bias: Some 1, High 1 I^2 = 0.00% Few participants (< 400)
Fear of falling	ES = 0.08 (-0.12 to 0.28)	406 (5 studies)	+++0[a] Moderate	Risk of bias: Some 2, High 4 I^2 = 0.00%

[a] Downgraded due to study limitations. [b] Downgraded due to inconsistency. [c] Downgraded due to imprecision.

Note: Under comments the main factors influencing the grading have been noted, but other factors have also been considered cf. the GRADE handbook

GRADE Working Group grades of evidence: **High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. **Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Figure 1

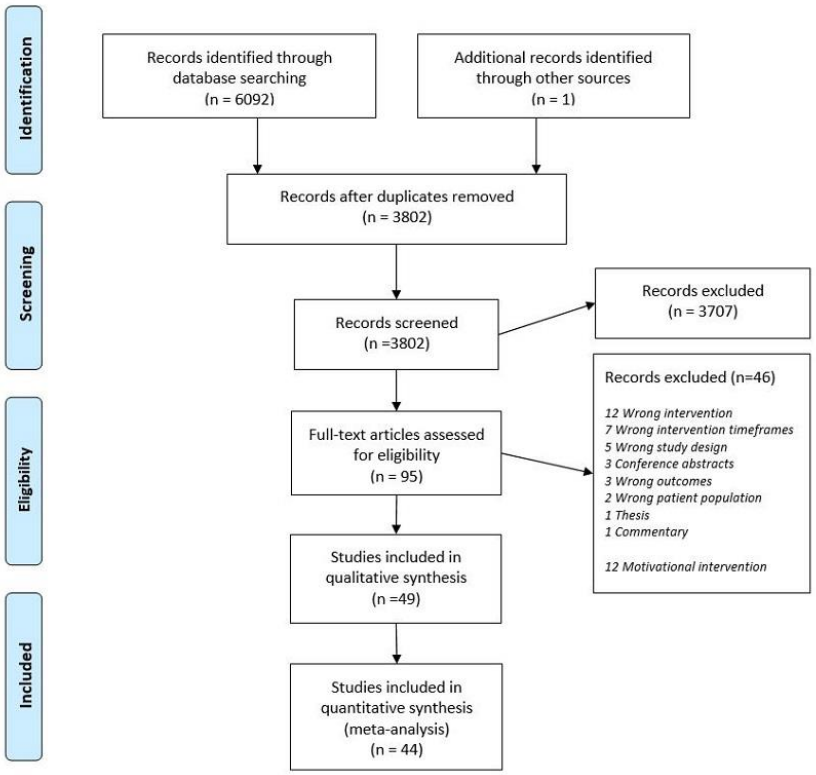


Figure 2

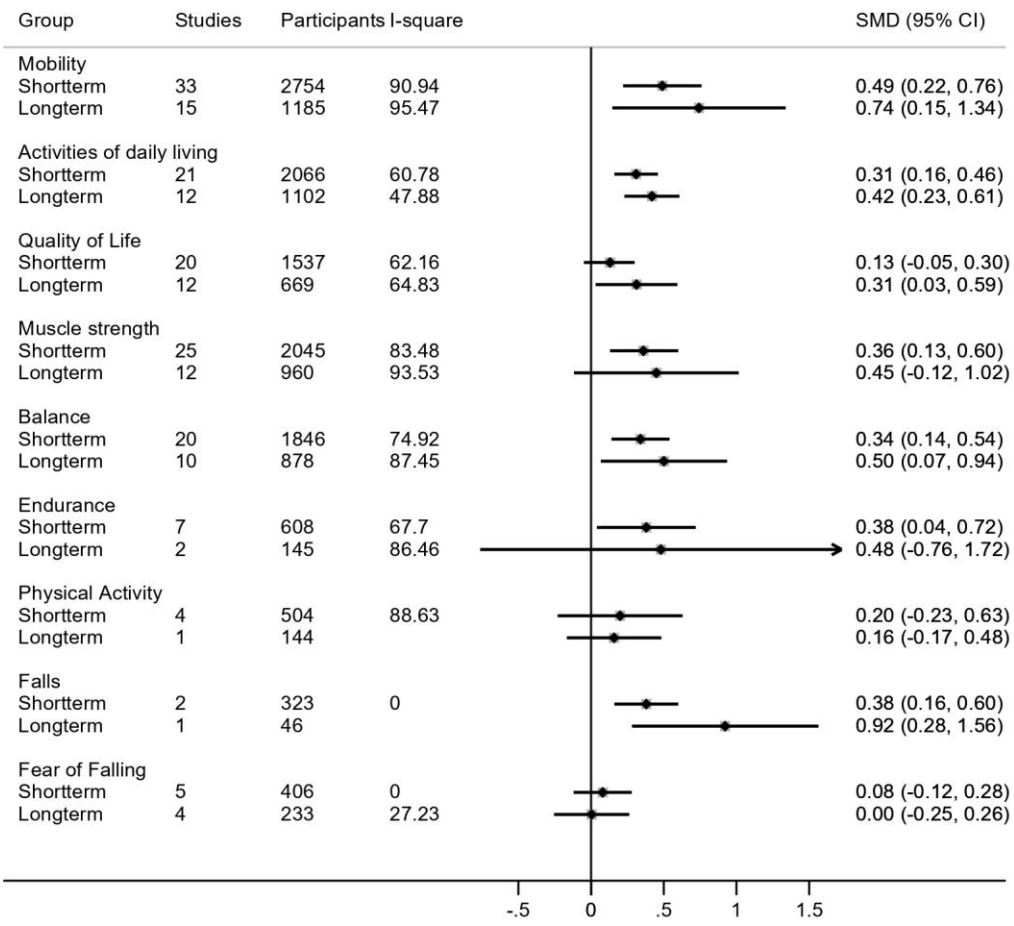


Figure 3

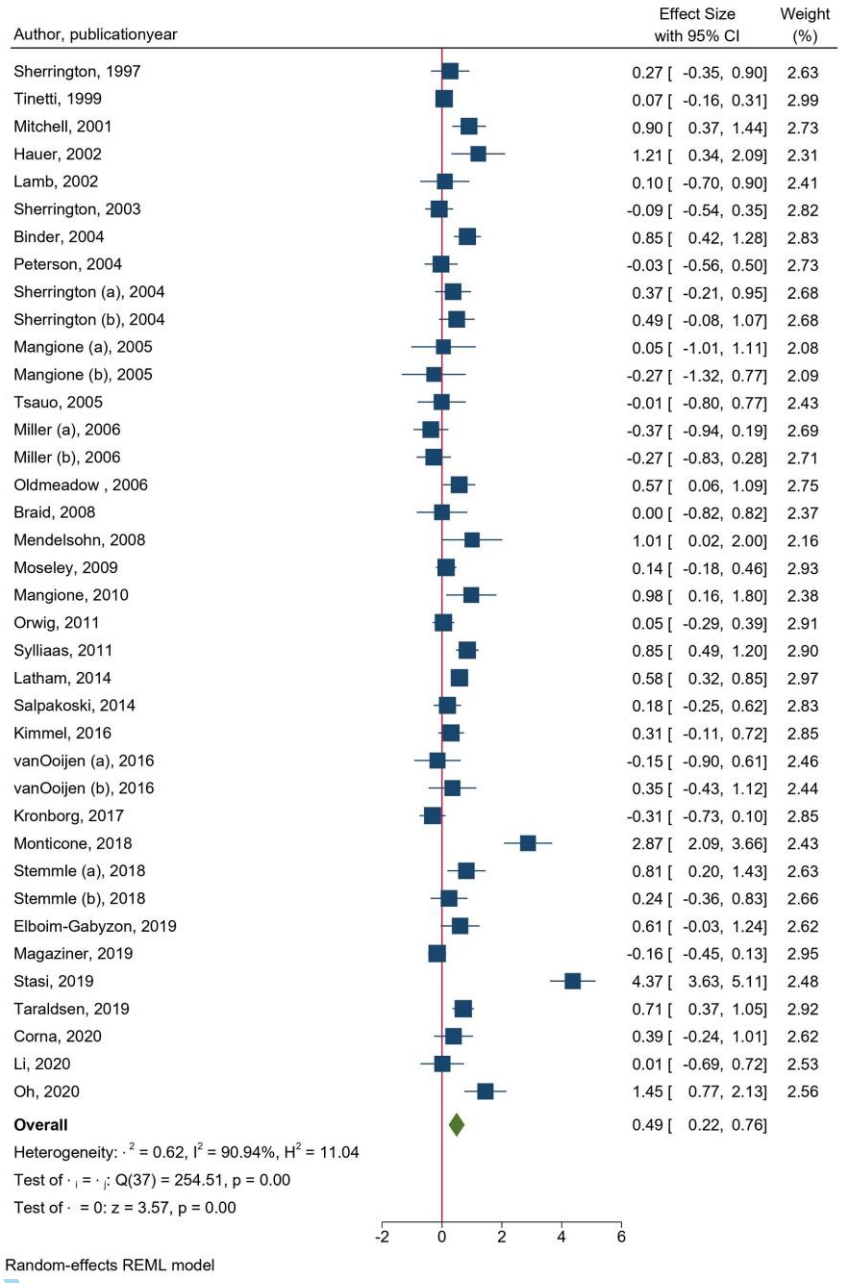
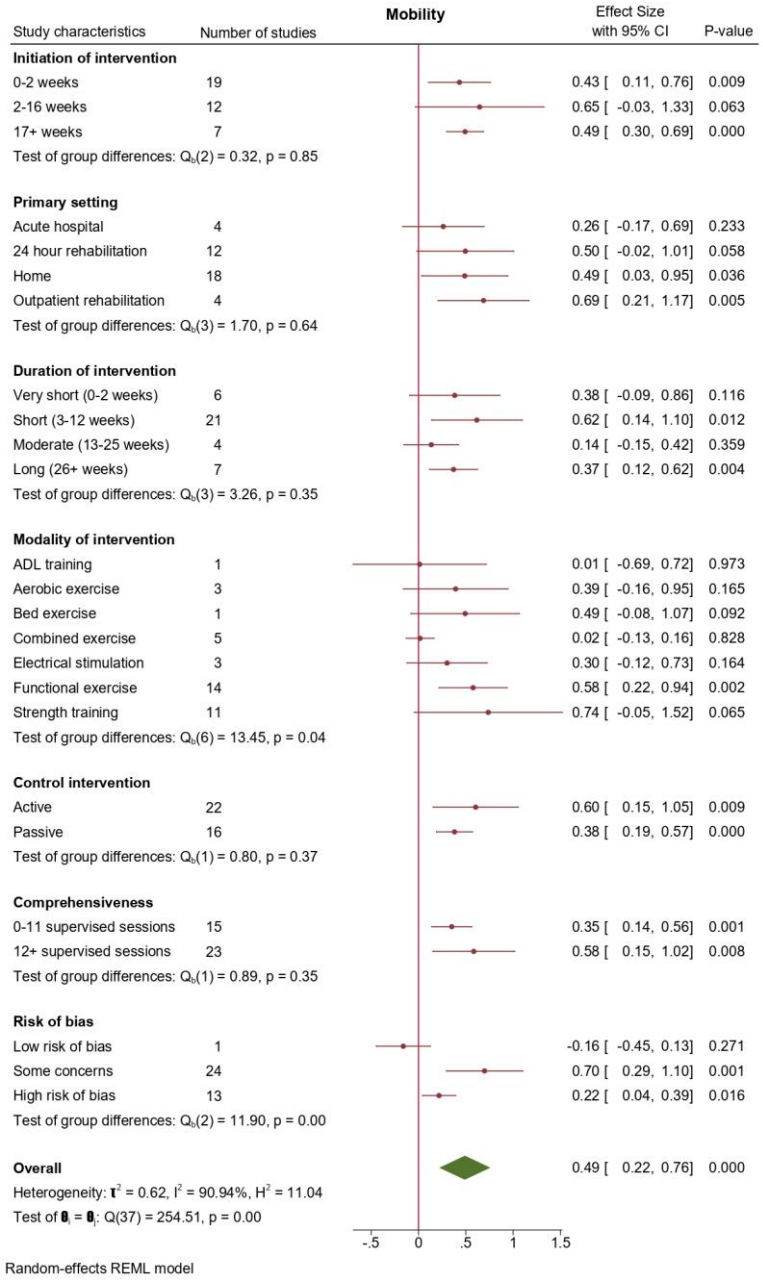


Figure 4



SUPPLEMENTARY MATERIAL

Overview of material

eMethods 1: Search query – Medline (Pubmed):

Search ((((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp]) OR randomly [tiab]) OR trial [ti])) OR ((Systematic review [pt]) OR Meta-analysis [pt]))) NOT ((animals [mh] NOT humans [mh])))) AND ((((((("hip fractures") OR "hip fracture") OR hip fractures[MeSH Terms]) OR femoral neck fractures[MeSH Terms])) OR (((((((("Femoral neck") OR Cervical) OR Trochanteric) OR Pertrochanteric) OR Peritrochanteric) OR Intertrochanteric) OR subtrochanteric)) AND ((((Fracture) OR Fractures) OR "Femoral fractures") OR "Femoral fracture")))) AND ((((((((((physical therapy modalities[MeSH Terms]) OR "physical therapy modality") OR "physical therapy modalities") OR Physiotherapy) OR "Physical therapy") OR "Physical therapies")) OR (((Occupational Therapy[MeSH Terms]) OR "Occupational Therapy") OR "Occupational Therapies")) OR ((((((((((Rehabilitation[MeSH Terms]) OR Rehabilitation) OR Exercise[MeSH Terms]) OR Exercise) OR Exercises) OR Exercise therapy[MeSH Terms]) OR "Exercise therapy") OR "Therapeutic exercise") OR "Therapeutic exercises") OR "physical training")) OR (("mobilisation") OR "mobilization")) OR ((((((((((((((((((((Physical fitness[MeSH Terms]) OR activities of daily living[MeSH Terms]) OR "activities of daily living") OR "activity of daily living") OR "strength training") OR "resistance training") OR "progressive resistance training") OR resistance training[MeSH Terms]) OR "endurance training") OR endurance training[MeSH Terms]) OR "Aerobic exercise") OR "Aerobic exercises") OR "Balance training") OR transcutaneous electrical nerve stimulation[MeSH Terms]) OR "transcutaneous electrical nerve stimulation") OR electric stimulation therapy[MeSH Terms]) OR "electric stimulation therapy") OR "early ambulation") OR "ADL training") OR "skilled training") OR independent living[MeSH Terms])))

eMethods 2: Description of exercise modalities

We divided exercise therapy into type of modality, based on our evaluation of the most predominant intervention modality or what differed the intervention from the control intervention. Some interventions were poorly described, and we recognize some subjectivity in our categorization.

In the below we describe modality characteristics:

ADL training: Intervention aiming at improving independency in activities of daily living (ADL) e.g. eating, bathing, dressing and ambulating.

Aerobic exercise: Aerobic exercise interventions with a description of intensity according to heart rate or VO2max.

Strength training: Interventions that applies to the RM principle or describes the intervention as moderate to high intensity using elastic bands, weight cuffs or body weight and has a load progression.

Combined exercises: Interventions combining strength training, aerobic training, balance training or functional exercises.

Functional exercise: Exercises involving training of the body for activities performed in daily life e.g. standing from chair, climbing step and walking on different surfaces. Balance training was included in this category, as balance training contains some of the same elements.

Electrical stimulation: Intervention applying transcutaneous electrical neuromuscular stimulation

Breathing exercise: Upper-body yoga including breathing exercises (1 trial).

Bed exercises: Non-weightbearing exercises in supine position (1 trial).

eTable 1: Table of study characteristics

Study Year Country	No. of partici-pants (int/con)	Age %Women (int/con)	Setting	Interven-tion Modality [a]	Initiation point of int.[b] (weeks)	Intervention D: Duration F: Frequency S: Session duration P: provider C: Comprehen-siveness[e]	Description of intervention and control	Follow-up time point[c]	Outcomes of interest[d]
Allegrante [i] 2007 USA	59 (32/27) *176 rand.*	Age:78/77 %W:75/78	Acute hospital and outpatient rehabilitation	Strength training	NI >6weeks	D: 8 weeks (outpatient) F: 2/week S: NI P: PT C: Yes	**INT:** Usual care + 1) In-hospital, postop. motivational video; a patient info booklet (falls-prevention, self-efficacy); supportive visit by recovered peer. 2) Out-patient program of tailored exercises (balance and gait retraining) and progressive muscle-strength training using free weights. Intensity was set at 60% of the 1-RM for the hip flexors and knee extensors and were progressively increased. **CON**: Usual postop. care + supportive telephone calls	- 6 months	-SF36 domain (physical functioning)
Baker 1991 Australia	40 (20/20)	Age:83/84 %W:100/ 100	Rehabilitation hospital	Functional exercise	NI (App. 2)	D: App. 8 weeks F: NC (>3/week) S: NC (Close to 15 min) P: PT C: Yes	**INT**: Gait retraining using a "Repco treadmill", with velocity and distance controls. Adjustable side rails for partial weight bearing stage. **CON**: Conventional gait retraining program. **Both**: Usual physiotherapy, incl. strength training before gait retraining phase.	- discharge from rehab hospital	-Knee extension muscle strength [g] -Mobility (3-level scale) [g]
Binder 2004 USA	90 (46/44)	Age:80/81 %W:72/77	Outpatient rehabilitation	Strength training	14	D: 6 months F: 3/week S: 45-90 min P: PT C: Yes	**INT:** Supervised exercise training initiated after end of standard physiotherapy. First 3 months small groups of 2-5, aimed at enhancing flexibility, balance, coordination, movement speed, and strength. 3-6 months progressive resistance training, 3 sets, 8-12 repetitions at 65-100% of initial 1-RM. **CON**: Low intensity home exercise program, focus on flexibility 3/week. Initiated after 1-hour session at the exercise facility, hereafter 1-hour group session every following month. Weekly phone calls. **Both**: Calcium and multivitamin tablets. D-vitamin if indicated. Dietician if indicated.	- 6 months	-Modified Physical Performance Test. -Functional Status Questionnaire -Knee extension strength -Bergs Balance Scale -SF-36 (health)
Bischoff-Ferrari [j] 2010 Switzerland	173 (87/86)	Age:83/85 %W:78/80	Acute hospital and home rehabilitation	Functional exercises	NI (App. 2)	D: 12 months F: 1/day S: 30 min P: PT C: No	**INT**: Unsupervised home exercises. Initiated under acute care with additionally 30 min home program instruction/day. Home exercise leaflet consisting of 4 exercises. **CON**: Standard physiotherapy under acute hospitalization. No home-program. **Both**: Equal proportion in each group were concurrent randomized to either standard 800	-12 months	-Falls [h] -Knee extensor strength bilat [g] -Timed Up and Go Test [g] -EQ-5D-3L index value *(reported in Renerts)*

							IU/d vitamin D3 therapy or 2000 IU/d vitamin D3 therapy.		
Braid 2008 UK	26 (15/11)	Age:81/80 %W:87/ 100	Rehabilitation hospital and outpatient rehabilitation	Electrical stimulation	2	D: 6 weeks F: 5/week (in-patient), 2 / week (after discharge) S: 18 min P: PT C: Yes	**INT**: Usual PT + electrical stimulation (ES) of the quadriceps muscle using two electrodes. ES consisted of 36 repetitions of cycles being 7 sec. stimulation and 23 sec. relaxation. **CON**: Usual PT while in-patient. Supervised strengthening, ROM exercises, balance training, transfers and gait re-education.	-6 weeks	-Leg extension power -Elderly Mobility Scale -Barthel Index -Nottingham Health Profile
Corna 2020 Italy	40 (20/20)	Age:84/86 %W:75/75	Rehabilitation Hospital	Aerobic exercise	2	D: 3 weeks F: 5/week S: 30 min P: PT C: Yes	I**NT**: Usual rehabilitation + individualized progressive aerobic exercise with an arm crank ergometer. Total 15 sessions. Intensity of 64% to 76% of maximum heart rate, and perceived exertion between 11 and 14 on Borg Scale. **CON**: Usual rehabilitation consisting of exercises for joint ROM, muscle strength, function, balance, gait and stair climbing. Total 15 sessions.	-3 weeks	-Timed Up and Go Test -Muscle torque of knee extensor fractured leg - Functional Independence Measure
Edgren[k] 2015 Finland	81 (40/41)	Age:81/79 %W:78/78	Home rehabilitation	Combined exercises	9	D: 12 months F: Strength/stretch 3/week, balance /functional 2-3 /week S: 30 min/session P: PT C: Yes	**INT**: Standard care + home exercises incl. strengthening (using elastic bands) and stretching for lower limp muscles, balance, and functional exercises. Program adjusted/progressed 4-5 times. Included 5-6 supervised sessions by a PT. Motivational counseling visits at 3 and 6 months, phone calls at 4 and 8 months. **CON**: Standard care including written home exercise program of 5-7 exercises. No progression over time.	-12 months	-Falls -Basic ADL
Elboim-Gabyzon 2019 Israel	41 (18/23) *44 rand.*	Age:78/80 %W:67/87	Acute Hospital	Electrical stimulation	1	D: 5 days F: 1/day S: 30 min P: PT C: No	**INT**: Standard PT + TENS. TENS was applied prior to walking Administered for 30 min during walking and a following rest period. **CON:** Standard PT + sham TENS. Standard PT consisted of transfer training, balance and lower extremity exercises and ambulation exercises.	-5 days	-Functional Ambulation Classification -Lower limb strength (5xSTS)
Hagsten 2004/2006 Sweden	100 (50/50)	Age:81/79 %W:84/76	Acute hospital and home visit before discharge	ADL training	1	D: 1 week F: Daily during weekdays S: 45-60 min P: OT C: No	**INT**: Usual care + OT training of activities with greatest importance to the patient's self-care and independence. Including technical aids and instructions related to transfer, walking and ADL. Home visit before discharge. **CON**: Conventional postoperative rehabilitation from nursing staff. No OT. **Both**: Instruction from PT on how to walk with crutches/walking frames.	-1 week -2 months	-The Klein-Bell ADL scale -Swedish Health-Related Quality of Life questionnaire
Hauer 2002	28 (15/13)	Age:82/81	Outpatient rehabilitation	Strength training	7	D: 12 weeks F: 3/week	**INT**: Supervised high-intensity progressive resistance training of lower limb muscle	-12 weeks -6 months	-Leg extension muscle strength

Germany		%W:100/ 100				S: 90+45 min P: Therapeutic recreation specialist C: Yes	groups and functional / balance training. Intensity of strength training was 70–90% of the individual maximal workload, 2-3 sets of 10-15 repetitions. Functional training was progressed with increasing complexity. Groups of 4-6 persons. **CON**: Motor placebo activities (calisthenics, games and memory tasks – seated) 3/week for 1 hour. **Both:** Massage, stretching and thermotherapy (2/week for 25 minutes).		-Timed up and Go Test -Barthel Index -Tinetti's POMA -The Philadelphia Geriatric Morale Scale -The Falls Handicap Inventory
Hermanky 2017 Austria	38 (18/20) *40 rand.*	Age:79/80 %W:67/65	Acute hospital	Strength training	1	D: 16,4 days F: 3-4/week S: 20 min P: PT C: No	**INT**: Standard therapy + moderate resistance exercise (Hip-, thigh-, buttocks-, upper arm-, shoulder muscles using own body weight and Thera-Bands. Additionally, protein optimized diet 1,5g/ kg bodyweight/day. **CON**: Standard therapy	-discharge -1 month thereafter	-Chair Rise Test (30sec)
Jinli 2019 China	79 (39/40) *84 rand.*	Age:74/75 %W:56/63	Acute hospital and home rehabilitation	breathing exercises	1	D: 4 weeks F: 2/day S: NI P: PT C: No	**INT**: Abdominal breathing exercises + Upper-body yoga incl. Instruction by PT and audio until able to carry out by audio alone. **CON**: Abdominal breathing exercises, instructed by a nurse and audio until able to carry out independently. **Both**: Exercise regime of lower body and systemic movement.	-4 weeks	-Barthel Index
Kimmel 2016 Australia	92 (46/46)	Age:81/81 %W:74/54	Acute Hospital	Functional exercises	1	D: 5 days F: 3/day S: 30 min/session P: PT and allied health assistant C: No	**INT**: 1/day usual physiotherapy + 2 additional daily sessions/day focused on improvement in independence and function/walking. **CON**: 1/day usual physiotherapy; individualized treatment focused on bed-based limb exercises and gait retraining, with goal of reaching early independent transfer and mobility.	-5 days -6 months	-Modified Iowa Level of Assistance Score -EQ-5D-5L
Kronborg 2017 Denmark	90 (45/45)	Age:80/79 %W:80/73	Acute Hospital	Strength training	1	D: 1 week F: 2/day S: mean 22 min P: PT C: No	**INT**: Usual PT + 1/day progressive fractured limb knee-extension resistance exercise using weight cuffs, 3 sets of 10 repetitions, intensity of 10 RM, 7/week. **CON:** Usual PT 1/day, focused on basic mobility independence and lower limb exercises.	-day 10 and/or at discharge.	-Knee-extension strength fractured limb in % of non-fractured limb. -Timed Up and Go Test -Falls Efficacy Scale International [g] -Physical activity, 24 hour (ActivePal) [g]
Lamb 2002 UK	24 (12/12) *27 rand.*	Age:83/84 %W:100/100	Hospital and Home rehabilitation	Electrical stimulation	1	D: 6 weeks F: 1/day S: 3 hours P: PT C: No	**INT:** Usual PT (inpatient) + Patterned neuromuscular stimulation (PNMS) of quadriceps fractured leg. Intensity was the min. required for a visible muscle contraction. **CON**: Usual PT (inpatient) + placebo stimulation with a sensory stimulus but	-7 weeks -13 weeks	-Leg extension power injured limb -Gait speed 3.05m -Tandem stand

							negligible muscle activation. 3 hours/day, 6 weeks.		
Latham 2014 USA	232 (120/112)	Age:77/79 %W:69/69	Home rehabilitation	Functional exercises	36	D: 6 months F: 3/week S: NI P: PT C: No	**INT**: Functionally oriented home exercises consisting of simple functional task using Thera Bands and weighted wests (such as standing from a chair, climbing a step). Additional cognitive-behavioral strategies were used. 3-4 supervised sessions otherwise performed independently. Participants were provided with a DVD-version of the program. **CON**: One home visit by a dietician providing nutritional cardiovascular education and an illustrated nutritional manual. **Both**: Monthly telephone calls.	-6 months -9 months	-Short Physical Performance Battery -Activity Measure for Post-Acute Care (daily activity subscale) -Lower extremity isometric muscle strength -Bergs Balance Scale
Lauridsen 2002 Denmark	88 (44/44)	Age:80/81 %W:100/1 00	Rehabilitation hospital	Combined exercises	3	D: 4 weeks F: 3/week S: 120 min P: PT C: Yes	**INT:** Standard exercise provided 2 hours/day, 3 days/week. Exercise: Strength, ROM, stretching and stabilizing exercises, gait, balance, stair climbing. **CON:** Standard exercises 15-30 min/day, 5 days/week	- discharge (app. 1 month)	Number of days until prespecified functional level was reached.
Li 2020 Hong Kong	31 (16/15)	Age:82/77 %W:69/93	Home rehabilitation	ADL Training	4	D: 3 weeks F: NI S: NI P: OT C: No	**INT**: Usual outpatient rehabilitation plus ADL home exercises on smartphone app. Frequency and duration of home program were jointly determined by OT and patient. Videos, pictures, written and verbal instructions were shown on the app. Video of the patient exercising and verbal feedback was uploaded following each session. **CON**: Usual outpatient rehabilitation incl. 1.5-hour conventional OT (2/week). Written home program with equivalent ADL training contents as provided for int-group. Feedback was logged on a sheet.	- 3 weeks - 6 weeks	-Timed Up and Go Test -Functional reach -Muscle strength fractures leg -Modified Barthel Index -The falls efficacy scale
Magaziner 2019 USA	210 (105/105)	Age:80/81 %W:76/77	Home rehabilitation	Combined exercises	14	D: 16 weeks F: 2-3/week S: 60 min P: PT C: Yes	**INT**: Supervised exercise focused strength, endurance, balance, and function. 4 progressive lower limb strength exercises using a portable device in 3 sets of 8 repetitions bilateral and load of app. 8 RM. Intensity was reassessed every 2 weeks. Endurance exercise app. 20 minutes and target intensity was 50% of heart rate reserve. **CON**: Seated active ROM exercises progressed from 3 to 20 repetitions/exercise. Additionally, sensory-level TENS bilateral to lower limb muscle groups. **Both:** 2000 IU of vitaminD3, 600 mg of calcium and a multivitamin daily for 40 weeks. Dietician counseling.	-16 weeks -40 weeks	-Distance walked in 6 min (6min-walk) -NHATS balance score -Isometric quadriceps strength non fractured leg -Modified Physical Performance test -Falls (at 40 weeks)

Mangione (a) 2005 USA	21 (11/10) *3 groups: 41 rand.*	Age:78/78 %W:64/80	Home rehabilitation	Strength training	17	D: 12 weeks F: First 8 weeks, 2/week, following 4 weeks, 1/week. S: 30-40 min P: PT C: Yes	**INT**: Progressive resistance exercises for hip extensors and abductors, knee extensors and ankle plantar flexors – bilaterally. Using a portable progressive resistive exercise machine and body weight. 3 sets of 8 reps at 8RM. Re-assessment of intensity every 2 weeks. Total of 20 sessions. **CON:** Biweekly mailing of non-exercise topics, and instructions of not to begin with exercise programs until end of study.	-12 weeks (CON after 8 weeks)	-Maximal summed isometric lower extremity strength -Free gait speed -6MWT -SF-36 (physical function)
Mangione (b) 2005 USA	22 (12/10) *3 groups 41 rand.*	Age:80/78 %W:75/80	Home rehabilitation	Aerobic exercise	17	D: 12 weeks F: first 8 weeks 2/week, following 4 weeks, 1/week S: 20 min P: PT C: Yes	**INT:** ROM warm-up. Walking on level surface and on stairs with an intensity of 65-75% of age-predicted maximal heart rate for 20 min. If not able to walk for entire 20 min, ROM exercises were performed at same intensity. **CON:** Biweekly mailing of non-exercise topics, and instructions of not to begin with exercise programs until end of study.	-12 weeks (Con 8 weeks)	-Maximal summed isometric lower extremity strength -Free gait speed -6MWT -SF-36 (physical function)
Mangione 2010 USA	26 (14/12)	Age:80/82 %W:86/75	Home rehabilitation	Strength training	24	D: 10 weeks F: 2/week S: 30-40 min P: PT C: Yes	**INT**: Progressive strengthen exercise for hip extensors and abductors, knee extensors and ankle plantar flexors bilaterally. Using a portable progressive resistive exercise machine and body weight. 3 sets of 8 repetitions. Intensity at 8 RM, re-evaluated every 2 weeks. **CON**: TENS of same muscle groups, intensity below motor threshold, but above sensory threshold.	-10 weeks -26 weeks	-Maximal summed isometric lower extremity strength -6MWT -Modified PPT -SF-36 (physical function)
Martin-Martin 2013 Spain	122 (61/61)	Age:81/83 %W:82/72	Acute hospital	ADL training	1	D: 1 week F: 1/day (on weekdays) S: first session 60 min hereafter 20 min P: OT C: No	**INT**: Standard care + OT focusing on strategies for autonomy recovery (transfer and ADL training, home environment advice, falls prevention). Brochure of training and information. **CON:** Standard care (medical and PT). PT was initiated day after surgery and provided 5 days/week for 30 min per session.	-1 month -6 months	-Goldberg General Health Questionnaire (GHQ-28) -Modified Barthel Index
Mendelsohn 2008 Canada	20 (10/10)	Age:80/81 %W:70/70	Rehabilitation hospital	Aerobic exercise	1	D: 4 weeks F: 3/week S: 30 min P: PT C: Yes	**INT:** Standard care (incl PT + OT) + Aerobic exercises using arm crank ergometer, warm-up 5 min, endurance phase 20 min (65% of baseline Vo2peak), cool-down 5 min. **CON**: Standard care (incl PT + OT daily on weekdays (45 min/session). Exercise consisted of ROM, flexibility, strengthening, gait, balance and ADL.	-4 weeks	-VO2 peak -Timed Up and Go Test -Bergs Balance Scale -Functional Independence Measure
Miller (a) 2006 Australia	49 (24/25) *4 groups*	Age:83/84 %W:71/84	Rehabilitation hospital and home rehabilitation	Strength training	1	D: 12w for exercise F: 3/week S: 20-30 min P: PT	**INT**: Nutritional supplement 6 weeks + Progressive resistance exercise for lower limb muscle groups using elastic bands. Increased	-12 weeks	-10-Meter Walk Test -Quadriceps strength injured leg -SF-12 (physical)

						C: Yes	when 2 sets of 8 reps could be completed in good form. **CON**: Daily Nutritional supplement for 6 weeks. Met 45% of individually estimated total energy requirements. From week 7-12, attention control visits matching contact in the resistance group.		
Miller (b) 2006 Australia	51 (25/26) *4 groups*	Age:85/83 %W:80/81	Rehabilitation hospital and home rehabilitation	Strength training	1	D: 12 weeks F: 3/week S: 20-30 min P: PT C: Yes	**INT:** Progressive resistance exercise for lower limb muscle groups using elastic bands. Increased when 2 sets of 8 reps could be completed in good form. **CON:** Attention control visits similar frequency as intervention group. General information, but no exercise.	-12 weeks	-10-Meter Walk Test -quadriceps strength injured leg -SF-12 (physical)
Mitchell 2001 UK	80 (40/40)	Age:81/79 %W:85/83	Rehabilitation hospital	Strength training	2	D: 6 weeks F: 2/week S: NI P: PT C: Yes	**INT:** Standard + Progressive resistance training of quadriceps bilateral. Week 1+2: Training was at 50% of the 1RM. Weeks 3+4: 1RM was reestablished, training at 70% of new 1RM. Weeks 5+6: 1RM re-established, Training at 80% of new 1RM. 3 sets of 12 reps of knee extension bilateral. 2 minutes rest between sets. **CON:** Standard treatment. PT 5 days/week, app. 20 min/day consisting of bed exercises and functional exercises (bed and chair transfers, gait re-education, and balance training).	-6 weeks -16 weeks	-Leg extension power -Elderly Mobility Scale -Functional Reach -Barthel Index -Nottingham Health Profile
Monticone 2018 Italy	52 (26/26)	Age:77/78 %W:73/69	Rehabilitation Unit	Functional exercises	2	D: 3 weeks F: 5/week S: 90 min P: PT C: Yes	**INT**: Progressed standing and walking balance task-specific exercises. Additional exercises such as 'sit to stand', stair climbing and climbing obstacles. **CON:** Open kinetic chain exercises in supine position aimed at improving ROM. 5/week for 90 min. **Both:** Booklet giving ergonomic advice.	-3 weeks -12 months	-WOMAC (physical function subscale) -Berg Balance Scale -Functional Independence Measure -SF-36
Moseley 2009 Australia	160 (80/80)	Age:84/84 %W:81/81	Rehabilitation Unit and home rehabilitation	Functional exercises	2	D: 16 weeks F: 2/day S: 30 min/session P: PT C: Yes	**INT**: High intensity weight-bearing exercises in addition to walking (treadmill with partial body weight/walking program). Progression by reducing support, increasing step block height, decreasing chair height and increasing the number of repetitions. Inpatient program followed by home visits + exercise program. Frequency of home visits gradually decreased. **CON**: Usual care, 5 exercises sitting or lying plus a small amount of walking. 30min/day for 4 weeks. Inpatient program followed by home visits + exercise program.	-4 weeks -16 weeks	-Isometric knee extension strength fractured leg -Physical Performance and Mobility Examination, PPME -Barthel Index -Max balance range test -EQ-5D -Modified Falls Efficacy scale -Falls

							Both: Usual post-operative mobilization in the ward, and usual rehabilitation by other health professionals.		
Oh 2020 Korea	38 (19/19) *45 rand.*	Age:77/81 %W:68/68	Rehabilitation Hospital	Functional ?	1	D: 2 weeks F: 5/week S: 20 min P: PT C: No	**INT**: Usual rehabilitation plus anti-gravity treadmill (AGT) on weekdays. Exercise day 1–5: AGT was applied with 50%–60% of body weight and a rate of 1.5 mph, 20 min. Exercise day 6–10: 70%–80% of body weight, and a rate of 1.5–1.8 mph, 20 min. **CON**: Usual PT (30 min) plus bed exercises (20 min) in supine position. **Both:** Daily individualized 30 min sessions of passive physical therapy (e.g. heat, massage, and ultrasound)	- 3 weeks - 6 months	-Koval -Bergs Balance Scale -EQ-5D -modified Barthel Index
Oldmeadow 2006 Australia	60 (29/31)	Age:79/80 %W:72/65	Acute hospital	Functional exercises	1	D: 1 week F: 1/day S: NI P: PT C: No	**INT**: Early ambulation group walked as soon as possible on POD 1 or 2. **CON:** Delayed ambulation group walked on POD 3 or 4. **Both**: The ambulation re-education program was the same for both groups including walking re-education, bed exercises and chest physiotherapy as indicated.	-7 days	-Walking distance (m)
Orwig 2011 USA	180 (91/89)	Age:83/82 %W:100/100	Home rehabilitation	Combined exercises	10	D: 12 months F: Aerobic 3/week Strength 2/week S: app. 30 min/session P: PT ass. /exercise trainer C: Yes	**INT:** Exercise Plus Program consisted of exercise and a self-efficacy component. Exercise part was 11 upper + lower limb exercises using TheraBand and/or weight cuffs. Increased until 3 sets, 10 repetitions. Aerobic exercise using a stair step, progressed with light ankle weights. The self-efficacy part had motivational, educational, cuing and self-modeling components. Supervision gradually decreased (max. 56 supervised sessions). **CON**: Usual care: Short hospital stay and approximately 2-4 weeks of rehabilitation.	-12 months	-Yale Physical Activity Scale (exercise part) -Lower Extremity Gain Scale -Timed walked -6-Min Walk Test -Global Balance -SF-36
Peterson[i] 2004 USA	70 (38/32) *108 rand.*	Age:79/78 %W:88/79	Acute hospital and outpatient rehabilitation	Strength training	14	D: 8 weeks (outpatient) F: 2/week S: 60 min P: PT (3) C:Yes	See Allegrante	- 6 months	-Quadriceps strength, right leg -Timed Up and Go Test -Functional Reach -6 Min Walk Test
Renerts [j] 2019 Switzerland	173 (87/86)	Age:83/85 %W:78/80	Acute hospital and home rehabilitation	Functional exercises	NI (App. 2)	D: 12 months F: 1/day S: 30 min P:PT C: No	See Bischoff-Ferrari	-12 months	-EQ-5D-3L

Resnick (a) 2007 USA	102 (51/51) *4 groups*	Age:82/80 %W:100/100	Home rehabilitation	Combined exercises	12	D: 12 months F: Aerobic 3/week Strength 2/week S: 30 min. (Supervised visits 60 min) P: PT ass. /exercise trainer C: Yes	**INT:** Usual care + 'Only exercise' component: 11 upper + lower limb exercises using TheraBand and/or weight cuffs. Increased until 3 sets, 10 repetitions. Aerobic exercise using a stair step, progressed with light ankle weights. Supervision gradually decreased (max. 38 supervised sessions). **CON**: Usual care: Short hospital stay and approximately 2-4 weeks of rehabilitation.	-2 months -12 months	-Step Activity Monitor (SAM) Number of steps taken in 48 hours)
Resnick (b) 2007 USA	106 (52/54) *4 groups*	Age:81/81 %W:100/100	Home rehabilitation	Combined exercises	12	D: 12 months F: Aerobic 3/week Strength 2/week S: 30 min. (Supervised visits 60 min) P: PT ass. /exercise trainer C: Yes	**INT:** Usual care + 'Exercise Plus Program' - exercise and a self-efficacy component. The exercise part was 11 upper + lower limb exercises using TheraBand and/or weight cuffs. Increased until 3 sets, 10 repetitions. Aerobic exercise using a stair step, progressed with light ankle weights. The self-efficacy part had motivational, educational, cuing and self-modeling components. Supervision gradually decreased (max. 38 supervised sessions). **CON:** usual care and 'Plus only' component: A self-efficacy intervention with motivational, educational, cuing and self-modeling components. Participants received a telephone call in weeks with no scheduled visits. Max anticipated visits 38.	-2 months -12 months	-Step Activity Monitor (SAM) Number of steps taken in 48 hours)
Salpakoski[k] 2014 Finland	81 (40/41)	Age:81/79 %W:78/78	Home rehabilitation	Combined exercises	9	D: 12 months F: Strength/stretch 3/week, balance /functional 2-3 /week S: 30 min/session P: PT C: Yes	See Edgren	-12 months	-SPPB -Bergs Balance Scale
Sherrington 1997 Australia	42 (21/21)	Age:80/77 %W:62/95	Home rehabilitation	functional exercise	28	D: 4 weeks F: 1/day S: NI P: PT C: No	**INT**: Weight-bearing stepping exercise using 1 or 2 telephone books. Height of stepping block and maximum number of reps was individually assessed. Number of reps increased gradually. Written description, photograph and a diary were provided. 2 supervised visits during intervention. **CON**: NI	-1 months?	-Quadriceps strength affected leg -Postural sway -Gait velocity
Sherrington 2003 Australia	80 (41/39)	Age:81/81 %W:66/69	Rehabilitation unit	Functional exercises	3	D: 2 weeks F: 5/week S: NI P: PT C: No	**INT**: 5 weight-bearing exercises. Progression by increasing number of reps, decreasing hand support, increasing height of stepping blocks, decreasing chair height. Number of reps varied from 5-30 per exercise.	-2 weeks	-Knee extensor muscle strength -Postural sway -Physical Performance and Mobility Examination

							CON: Non-weightbearing exercises in supine position. Progressed by increasing number of reps. **Both**: Usual care + PT (walking and transfers).		
Sherrington (a) 2004 Australia	80 (40/40) *3 groups: 120 rand.*	Age:80/77 %W:75/85	Home rehabilitation	Functional exercises	20	D: 16 weeks F: 1/day S: NI P: PT C: No	**INT**: 5 weight-bearing exercises. Progression by increasing numb. of reps, decreasing hand support, increasing height of stepping blocks, decreasing chair height. Number of reps varied from 5-30 for a single exercise. Drawings were provided and 4 home visits conducted. **CON:** No intervention	-4 months	-Knee extensor muscle strength -Postural sway -Physical Performance and Mobility Examination
Sherrington (b) 2004 Australia	80 (40/40) *3 groups: 120 rand.*	Age:79/77 %W:78/85	Home rehabilitation	Bed exercises	20	D: 16 weeks F: 1/day S: NI P: PT C: No	**INT**: Non-weightbearing exercises in supine position. Progression by increasing number of repetitions. Number of repetitions varied from 5-30 per exercise. Drawings were provided and 4 home visits conducted. **CON:** No intervention	-4 months	-Knee extensor muscle strength -Postural sway -Physical Performance and Mobility Examination
Singh 2012 Australia	124 (62/62)	Age:80/78 %W:69/68	Outpatient rehabilitation	Strength training	7	D: 12 months F: 2/week S: NI P: Research staff (PT?) C: Yes	**INT:** Usual care + Progressive resistance training (80% of peak upper and lower body muscle strength). 7 machines, 3 sets, 8 reps, 80% of 1 RM (1 RM assessment every month). Program initiated after ceased standard PT. Monthly phone call and a monthly home visit by trainer. Total 80 supervised sessions, 10 home visits, and 10 phone calls. **CON**: Usual care, including orthogeriatric care, rehabilitation service, other medical and allied health consultation as required and physiotherapy.	-12 months	- Functional Independence Measure
Stasi 2019 Greece	96 (48/48) *100 rand.*	Age:78/78 %W:75/75	Acute inpatient + home rehabilitation	Strength training	4	D: 12 weeks F: First week 1/day, Week 2-12 3/week S: 40-55 min P: PT C: Yes	**INT**: Standard PT + Abductor strength training of fractured leg. Initiated from 4th postop. week with upright exercises. Week 7 progressing to exercises using elastic bands and weight cuffs. Inpatient for 1 week, homebased for 11 weeks. Written instructions. Visits by PT every fortnight until 6-month follow-up. **CON:** Standard PT for 12 weeks, frequency as intervention group. Intensity progressed gradually. Elastic bands from week 9. Written instructions. Visits by PT every fortnight until 6-month follow-up.	-3 months -6 months	-Lower Extremity Functional Scale -Isometric hip abductor strength fractured leg -Timed Up and Go Test
Stemmle [j] (a) 2018 Switzerland	87 (43/44)	Age:83/86 %W:79/80	Acute hospital and home rehabilitation	Functional exercises	NI (App. 2)	D: 12 months F: 1/day S: 30 min P: PT	**INT**: Unsupervised home exercises. Initiated under acute care with additionally 30 min home program instruction/day. Home exercise	-12 months	-Timed Up and Go Test -Knee extensor strength -SF-36 physical *(QoL reported in Renerts)*

						C: No	leaflet consisting of 4 exercises. Plus 800 IU of vitamin D3. **CON**: Standard physiotherapy under acute hospitalization. No home-program. Plus 800 IU of vitamin D3.		
Stemmle [j] (b) 2018 Switzerland	88 (44/44)	Age:84/86 %W:77/80	Acute hospital and home rehabilitation	Functional exercises	NI (App. 2)	D: 12 months F: 1/day S: 30 min P: PT C: No	**INT**: Unsupervised home exercises. Initiated under acute care with additionally 30 min home program instruction/day. Home exercise leaflet consisting of 4 exercises. Plus 2000 IU of vitamin D3. **CON**: Standard physiotherapy under acute hospitalization. No home-program. Plus 800 IU of vitamin D3.	-12 months	-Timed Up and Go Test -Knee extensor strength -SF-36 physical *(QoL reported in Renerts)*
Suominen[k] 2019 Finland	81 (40/41)	Age:81/79 %W:78/78	Home rehabilitation	Combined exercises	9	D: 12 months F: Strength/stretch 3/week, balance /functional 2-3 /week S: 30 min/session P: PT C: Yes	See Edgren	-12 months	-Physical activity (modified Grimsby Scale) (*Reportet in Turunen)* -SPPB *(Reported in Salpakoski)* -Isometric knee ext. force [g]
Sylliaas 2011 Norway	150 (100/50)	Age:82/83 %W:85/76	Outpatient rehabilitation	Strength training	12	D: 12 weeks F: 3/week (2 outpatient, 1 home) S: 45-60 min. P: PT C: Yes	**INT**: Progressive resistance training. Both outpatient and home exercise. 4 lower limb exercises. Initially 3 sets of 15 reps of 70% of 1 RM. After 3 weeks 80% of 1-RM. Every 3rd week reps were reduced first 12 then 10 until maintaining 8 reps. 1-RM was measured every 3rd week. Advised to walk 30 min/day. **CON:** No intervention, maintain current lifestyle, no restriction on exercise activities.	-6 months	-Bergs Balance scale -Sit-to-stand test -Timed Up and Go Test -6MWT -Nottingham extended Activities of daily living Scale -SF-12
Sylliaas 2012 Norway	95 (48/47)	Age:82/82 %W:82/81	Outpatient rehabilitation	Strength training	24	D: 12 weeks F: 2/week (1 outpatient, 1 home) S: 45-60 min P: PT C:Yes	**INT:** Additional progressive resistance training. Both outpatient and home exercise. 4 lower limp exercises. Initially 3 sets of 15 reps of 70% of 1 RM. After 3 weeks 80% of 1-RM. Every 3rd week reps were reduced to first 12 then 10 until maintaining 8 reps. 1-RM was measured every 3rd week. Outpatient sessions 1/week and home exercise 1/week. Advised to walk 30 min/day. **CON:** No intervention.	-9 months	-Bergs Balance Scale -Sit-to-stand test -Timed Up and Go Test -6MWT -Nottingham extended Activities of daily living Scale - SF-12
Taraldsen 2019 Norway	143 (70/73)	Age:84/83 %W:77/77	Home rehabilitation	Functional exercises	16	D: 10 weeks F: 2/week S: NI P: PT C: Yes	**INT:** Usual rehabilitation up to 4 months plus supervised home exercises of 5 individually tailored weight-bearing exercises: walking, stepping in a grid pattern, stepping up on a box, sit-to-stand, and lunge. Exercise was described at 5 increasing levels. Starting levels and progression were individually decided on.	-2 months -8 months	- 24 hours Physical activity (ActivePAL) -SPPB -Barthel Index -EQ-5D-3L -Short Form Falls Efficacy Scale International

							CON: Usual rehabilitation up to 4 months post-surgery.		
Tinetti 1999 USA	304 (148/156)	Age:81/79 %W:83/81	home rehabilitation	Combined exercises	4	6 months F: 1/day S: NI P: PT+OT C: Yes	**INT**: Combined physiotherapy and OT-based functional therapy. PT exercises: strength, balance, transfers, gait, and stair climbing. Instruction by therapist followed by daily unsupervised exercise. PT instruction 3/week the first 1-2 weeks and decreased gradually to 1-3 times/month. OT-based functional therapy: E.g. use of adaptive equipment, environmental modifications, psychological interventions to enhance confidence or motivation, education. Visits 1-2/week **CON:** Usual PT provided by home care agencies. Few participants received OT.	-6 months -12 months	-Proportion recovering prefracture basic ADL -Modified Bergs Balance Scale -Timed walk -Knee extensor strength non fractured leg
Tsauo 2005 Taiwan	25 (13/12) *54 rand.*	Age:74/72 %W:73/84	Home rehabilitation	Combined exercises	2	D: 12 weeks F: NI ?? S: NI P: PT C: No	**INT**: Home-based lower limb strengthening exercises, ROM exercises; balance training; functional training, ambulation training, and stair climbing; modification of home environment. Adjusted to individual capacity. 8 home visits by PT at week: 0,1,2, 3, 4, 6, 8, and 12. Average of 5 exercise items were taught at each visit, initially in 3 sets of 10 repetitions /day for each item. Intensity increased if tolerated. **CON**: No intervention	-3 months - 6 months	-Knee extensor strength -Walking speed -WHO-QOL-BREF
Turunen[k] 2017 Finland	81 (40/41)	Age:81/79 %W:78/78	Home rehabilitation	Combined exercises	9	D: 12 months F: Strength/stretch 3/week, balance /functional 2-3 /week S: 30 min/session P: PT C: Yes	See Edgren	-12 months	-Physical activity (modified Grimsby Scale) -SPPB (*reported in Salpakoski)*
vanOoijen (a) 2016 Netherlands	47 (24/23) *3 groups:* *70 rand.*	Age:83/67 %W:67/91	Rehabilitation unit	Functional exercise	2	D: 6 weeks F: 5/week S: 20 min P: PT C: Yes	**INT**: Usual PT (15 sessions) plus adaptability treadmill (AT) (15 sessions). AT: Comfortable walking speed, handrail for support. Exercises consisted of visually guided stepping to regularly/irregularly spaced stepping targets, obstacle avoidance, speeding up and slowing down, walking adaptability games consisting of interactive stepping targets and obstacles. **CON**: Usual PT (30 sessions, 5/week) including exercises of leg strength, balance, transfers, walking and ADL.	-6 weeks - 12 months	-The Performance Oriented Mobility Scale -Elderly Mobility Scale -The Nottingham Extended Activities of Daily Living scale -Falls Efficacy Scale International -Perceived general health -Number of fallers(12mo)

vanOoijen (b) 2016 Netherlands	46 (23/23) *3 groups: 70 rand.*	Age:84/83 %W:61/91	Rehabilitation unit	Functional exercise	2	D: 6 weeks F: 5/week S: 20 min P: PT C: Yes	**INT:** Usual PT (15 sessions) plus conventional treadmill (CT) (15 sessions). CT: Comfortable walking speed. Focus on quality and safety in walking, secondary on walking speed and distance. Handrail for support. **CON**: Usual PT group received 30 sessions, 5/week, including exercises of leg strength, balance, transfers, walking and ADL.	-6 weeks - 12 months	-The Performance Oriented Mobility Scale -Elderly Mobility Scale -The Nottingham Extended Activities of Daily Living scale -The Falls Efficacy Scale International -Perceived general health -Number of fallers(12mo)

Note. Rand: randomized, NC: not clear, NI: no information, OT: occupational therapy, PT: physiotherapy, ROM: range of motion, 1-RM: 1 repetition max, reps: repetitions

[a] Primary component of the intervention. [b] Timepoint from where the primary component of the intervention was initiated post-surgery. If no information, an estimation is given. [c] Follow up time from baseline. [d] Outcomes relevant for this systematic review and meta-analysis. [e] Comprehensiveness: 0-11 supervised sessions= No; 12+ supervised sessions= Yes. [f] Syllias 2012, not included in meta-analysis avoid “double-counting”. [g] Data not available for meta-analysis. [h] Data not relevant for meta-analysis. [i] Study population in Allegrante is also part of Peterson (2004). [j] Same study population in Bischoff-Ferrari (2010), Renerts (2019), Stemmle (2018). [k] Same study population in Salpakoski (2014), Edgren (2015), Suominen (2019), Turunen (2017).

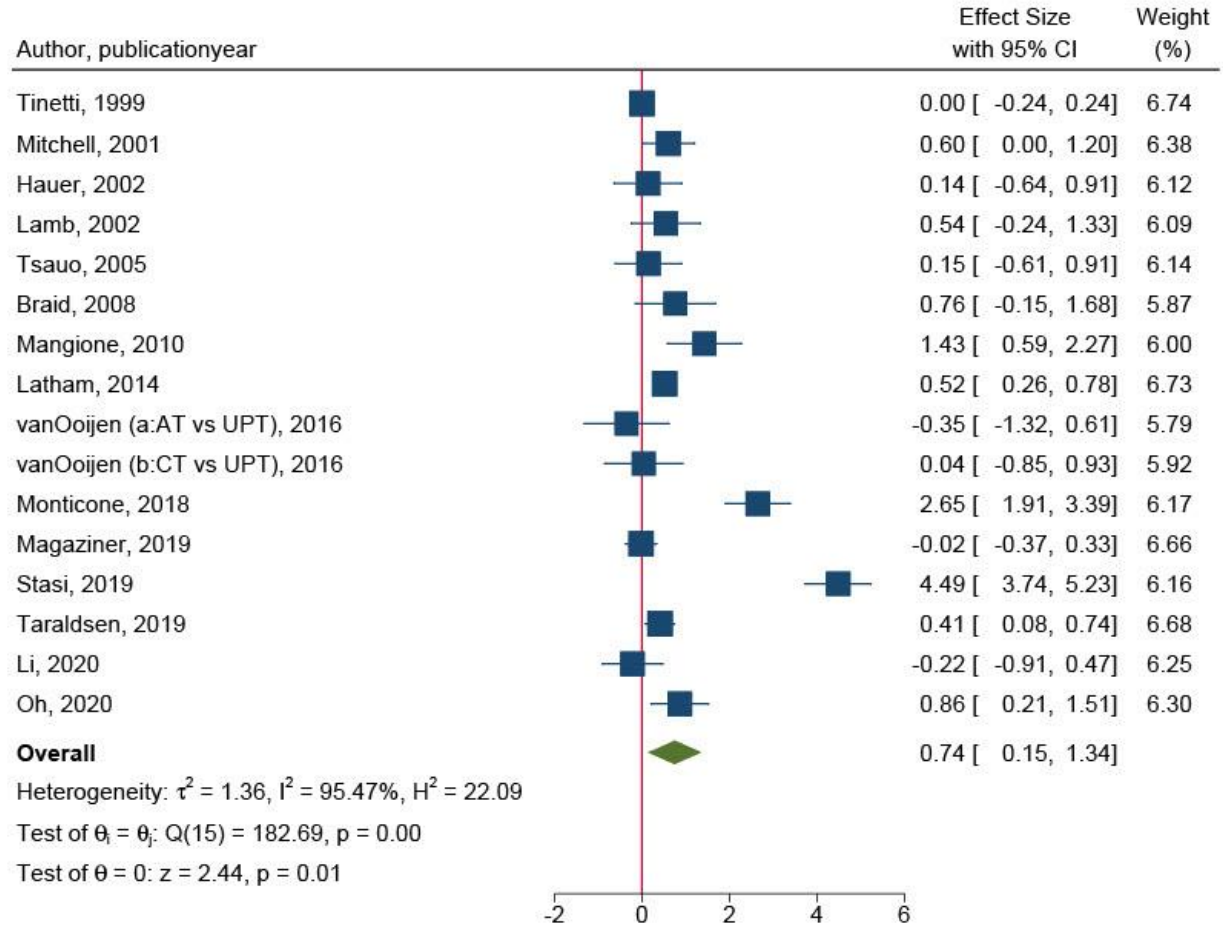
eTable 2: Risk of bias assessment using the Cochrane Risk of Bias Tool (ROB2)										
Study	**Risk of bias domain**									**Outcome Measure[a]**
	1	**2**	**3**	**4**		**5**		**Overall**		
				O	**P**	**O**	**P**	**O**	**P**	
Allegrante (2007)				-		-		-		SF36
Peterson (2004)					-		-		-	TUG
Baker (1991)					-		-		-	Mobility
Binder (2004)										mPPT/FSQ
Bischoff-Ferrari (2010)				-		-		-		Falls
Renerts (2019)				-		-				EQ5D
Stemmle (2018)										TUG/SF36
Braid (2008)										EMS/NHP
Corna (2020)					-		-		-	TUG
Elboim-Gabyzon (2019)					-		-		-	FAC
Hagsten (2004)										Klein-Bell/SWED-QUAL
Hauer (2002)										TUG/PGCMS
Hermanky (2017)					-		-		-	Chair rise
Jinli (2019)					-		-		-	Barthel
Kimmel (2016)										mILOA/EQ5D
Kronborg (2017)					-		-		-	TUG
Lamb (2002)					-		-		-	Gait speed
Latham (2014)										SPPB/AM-PAC
Lauridsen (2002)					-		-		-	Mobility
Li (2020)										TUG/FES
Magaziner (2019)					-		-		-	mPPT
Mangione a(2005)										Gait speed/SF36
Mangione b(2005)										Gait speed/SF36
Mangione (2010)										mPPT/SF36
Martin-Martin (2013)				-		-		-		mBI
Mendelsohn (2008)					-		-		-	TUG
Miller (2006)										10MWT/SF12
Mitchell (2001)										EMS/NHP
Monticone (2018)										Berg/WOMAC
Moseley (2009)										PPME/EQ5D
Oh (2020)										Koval
Oldmeadow (2006)					-		-		-	Walk distance
Orwig (2011)										LEGS/YPAS
Resnick (2007)					-		-		-	SAM
Salpakoski (2014)					-		-		-	SPPB
Edgren (2015)				-		-		-		B-ADL
Turunen (2017)				-		-		-		Grimsby scale
Sherrington (1997)					-		-		-	Gait velocity
Sherrington (2003)					-		-		-	PPME
Sherrington (2004)					-		-		-	PPME
Singh (2012)					-		-		-	FIM
Stasi (2019)										TUG/LEFS

Sylliaas (2011)										TUG/NEADL
Syllias (2012)										TUG/SF12
Taraldsen (2019)										SPPB/EQ5D
Tinetti (1999)										Timed walk/B-ADL
Tsauo (2005)										Walking speed/WHO-QoL
vanOoijen (2016)										EMS/General health

[a] The outcome measure(s) for which the effect estimate was assessed for risk of bias.

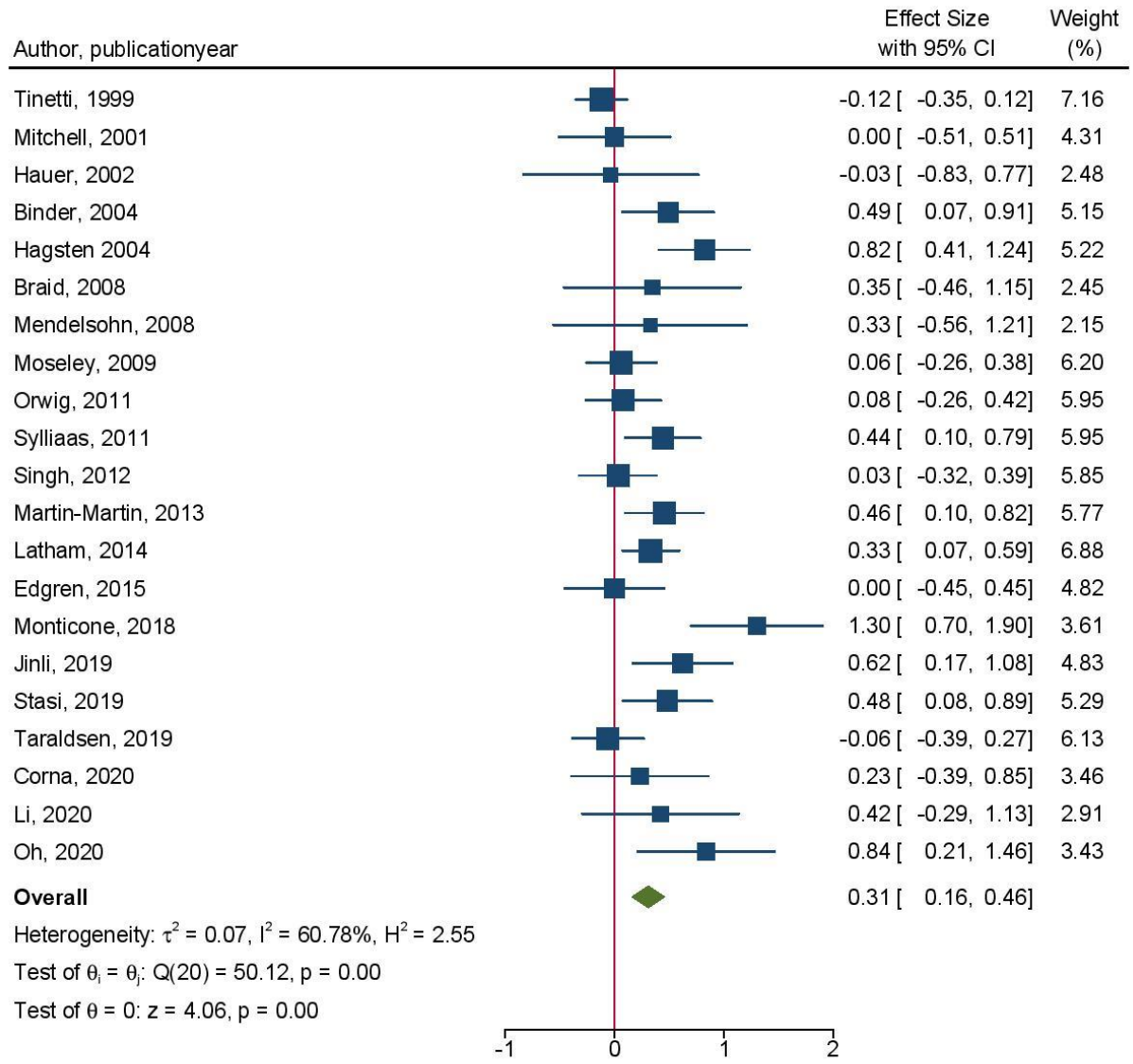
Note. O=objective, P=patient-reported
1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result.

eFigure 1: Forest plot of the effect of exercise therapy on mobility at long-term.



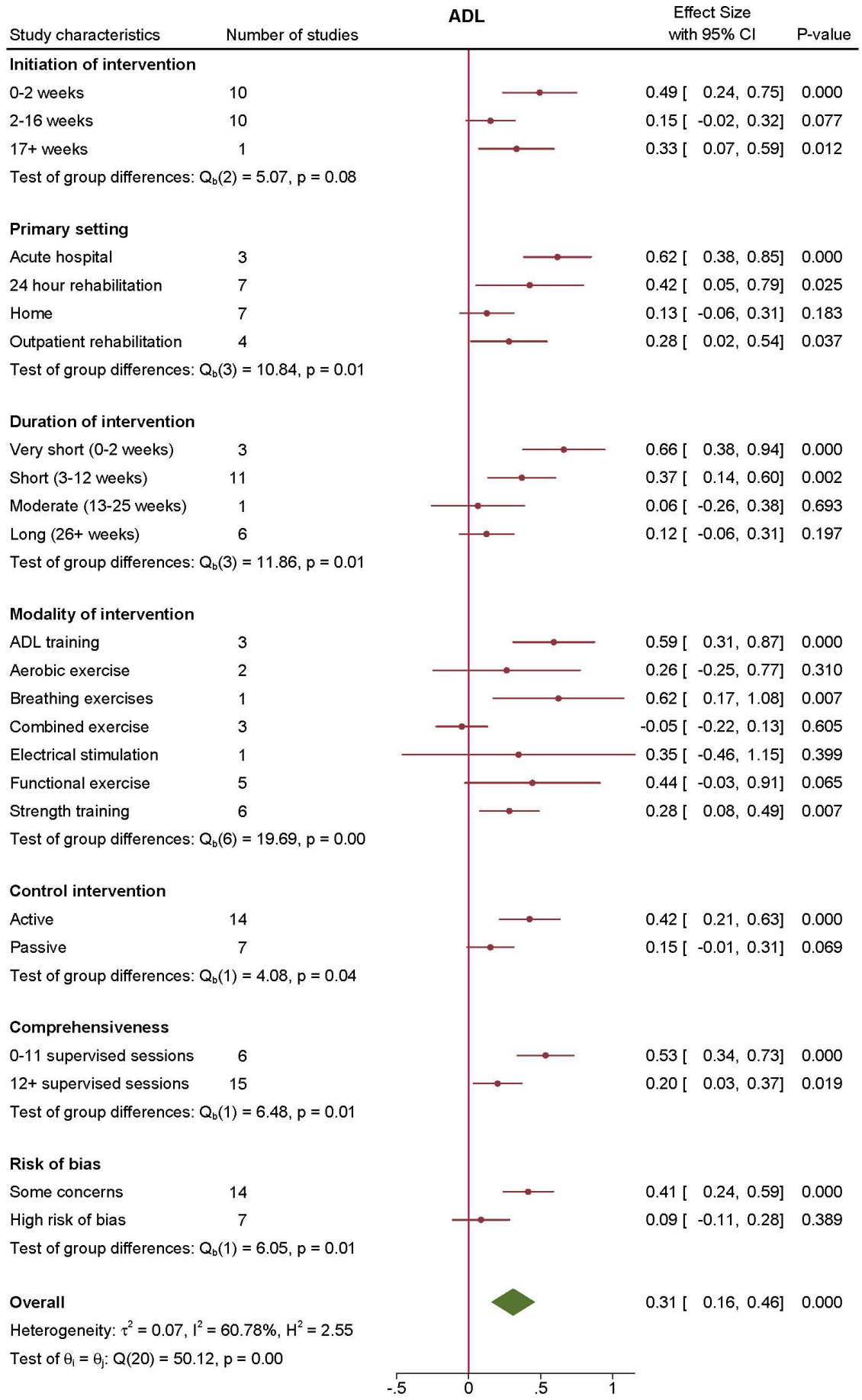
Random-effects REML model

eFigure 2: Forest plot of the effect of exercise therapy on ADL at short-term.



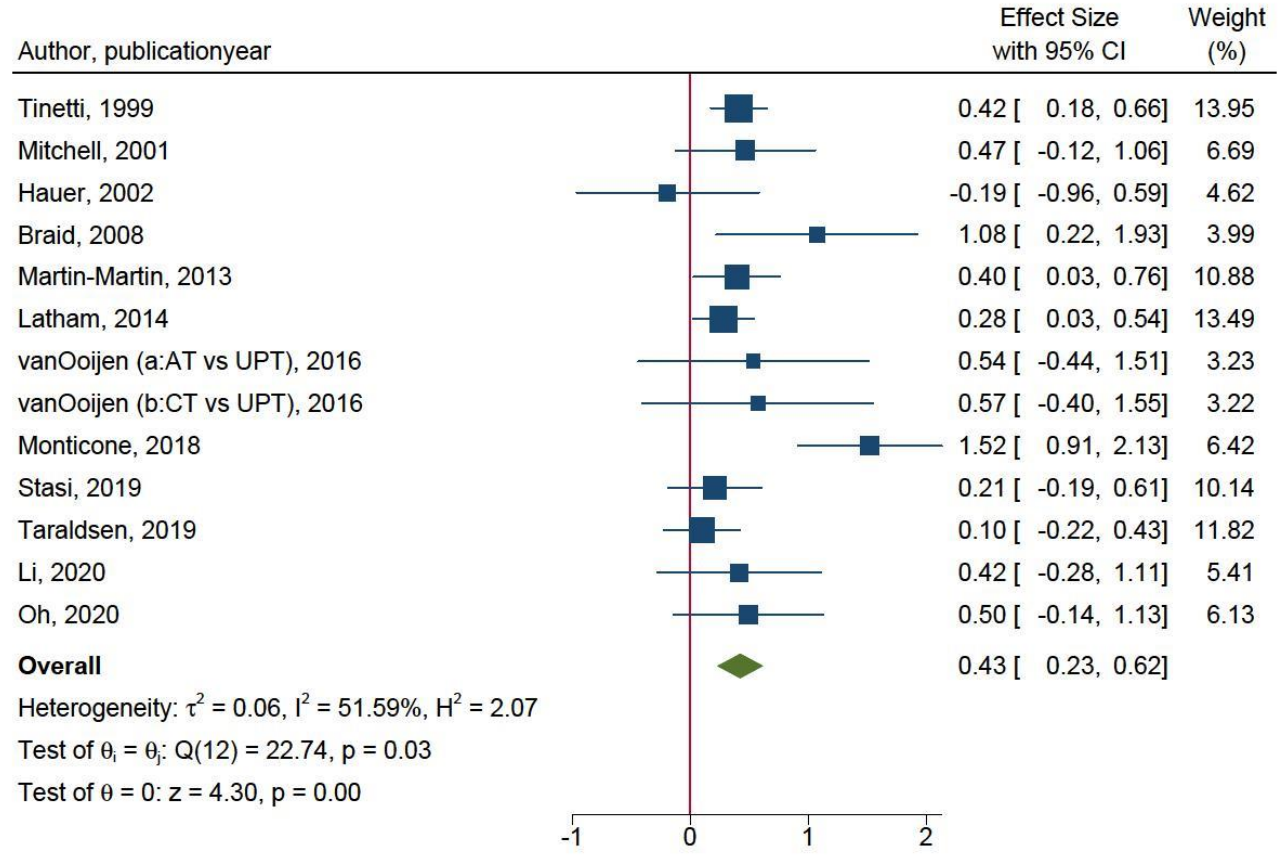
Random-effects REML model

eFigure 3: Subgroup analysis of the effect of exercise therapy on ADL

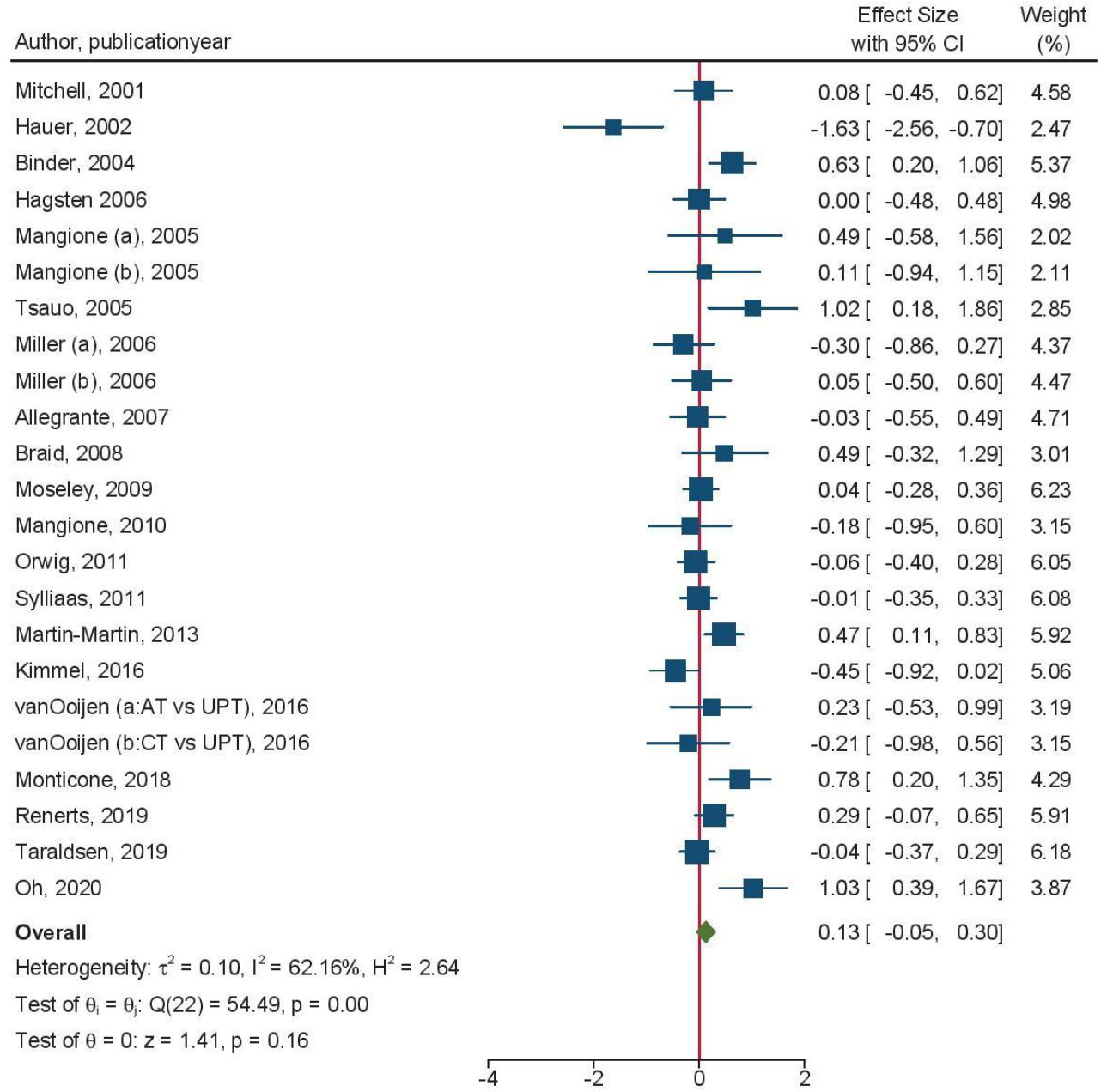


Random-effects REML model

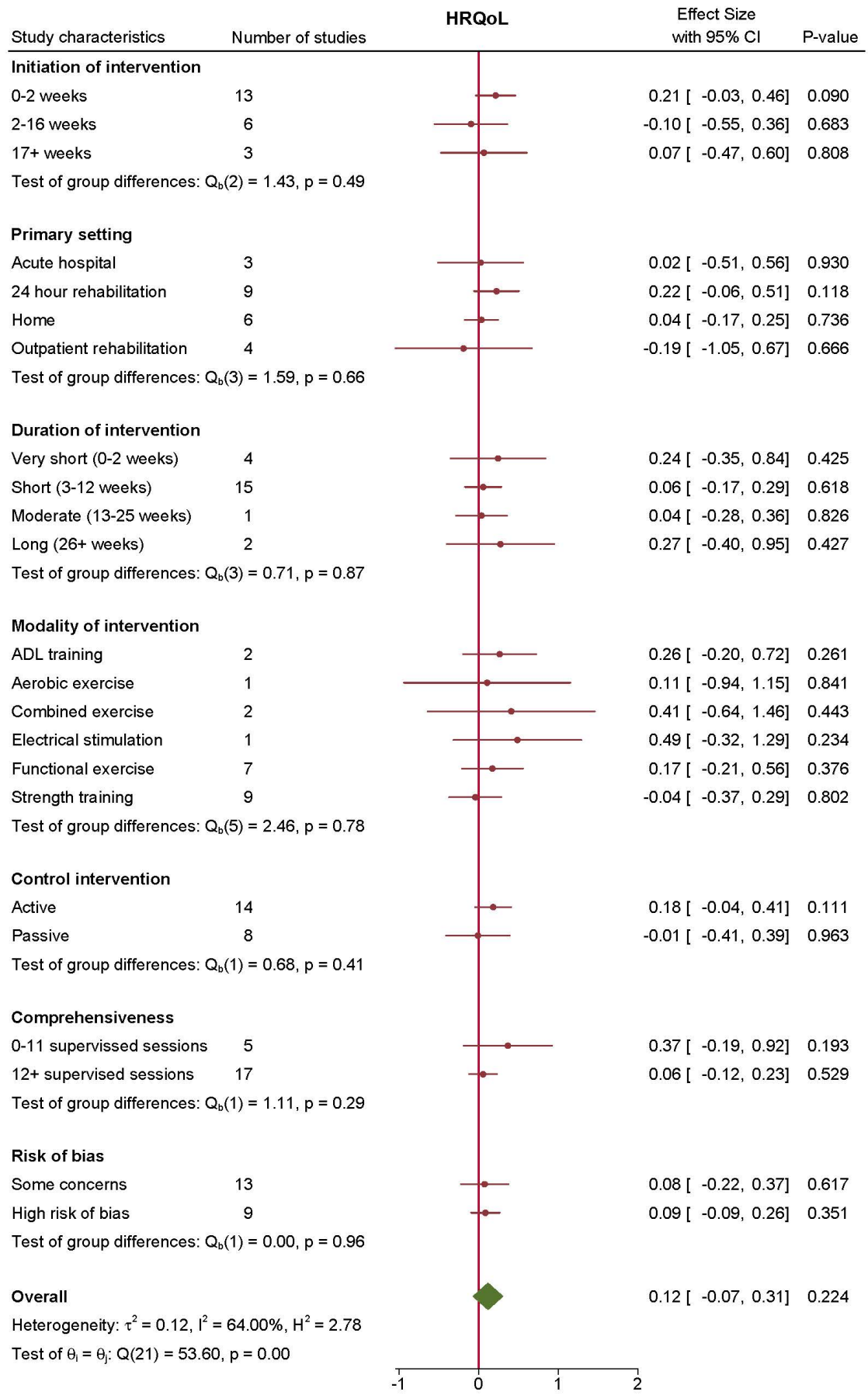
eFigure 4: Forest plot of the effect of exercise therapy on ADL at long-term.



eFigure 5: Forest plot of the effect of exercise therapy on HRQoL at short-term.

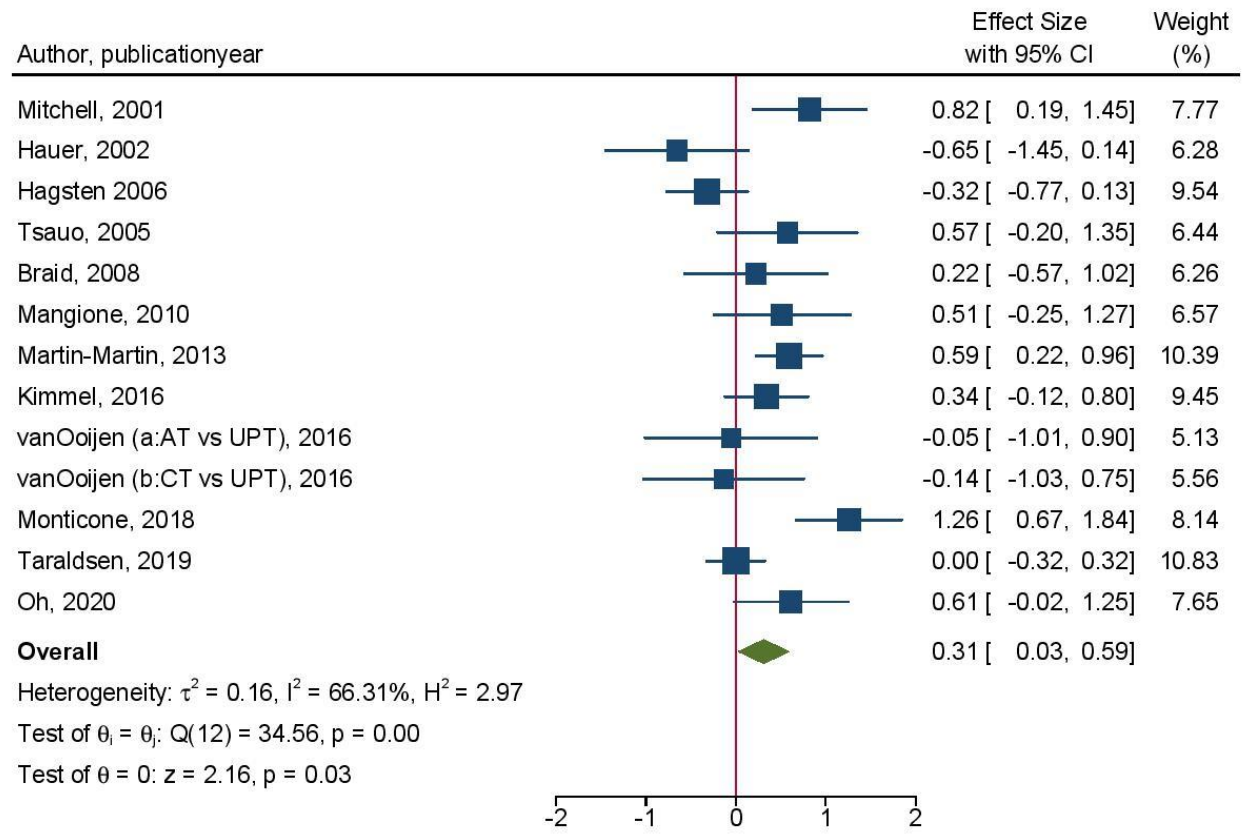


eFigure 6: Subgroup analysis of the effect of exercise therapy on HRQoL.

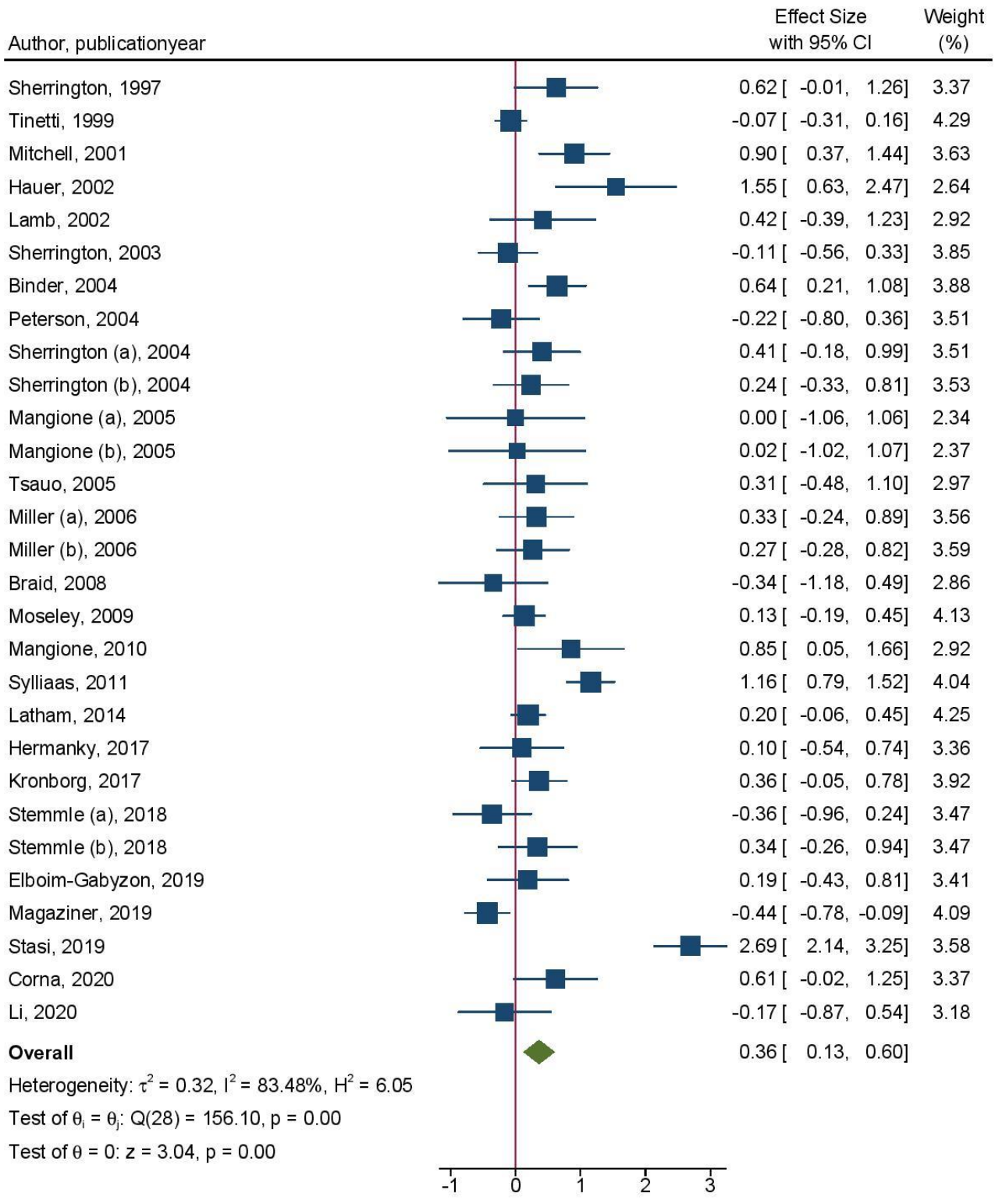


Random-effects REML model

eFigure 7: Forest plot of the effect of exercise therapy on HRQoL at long-term.

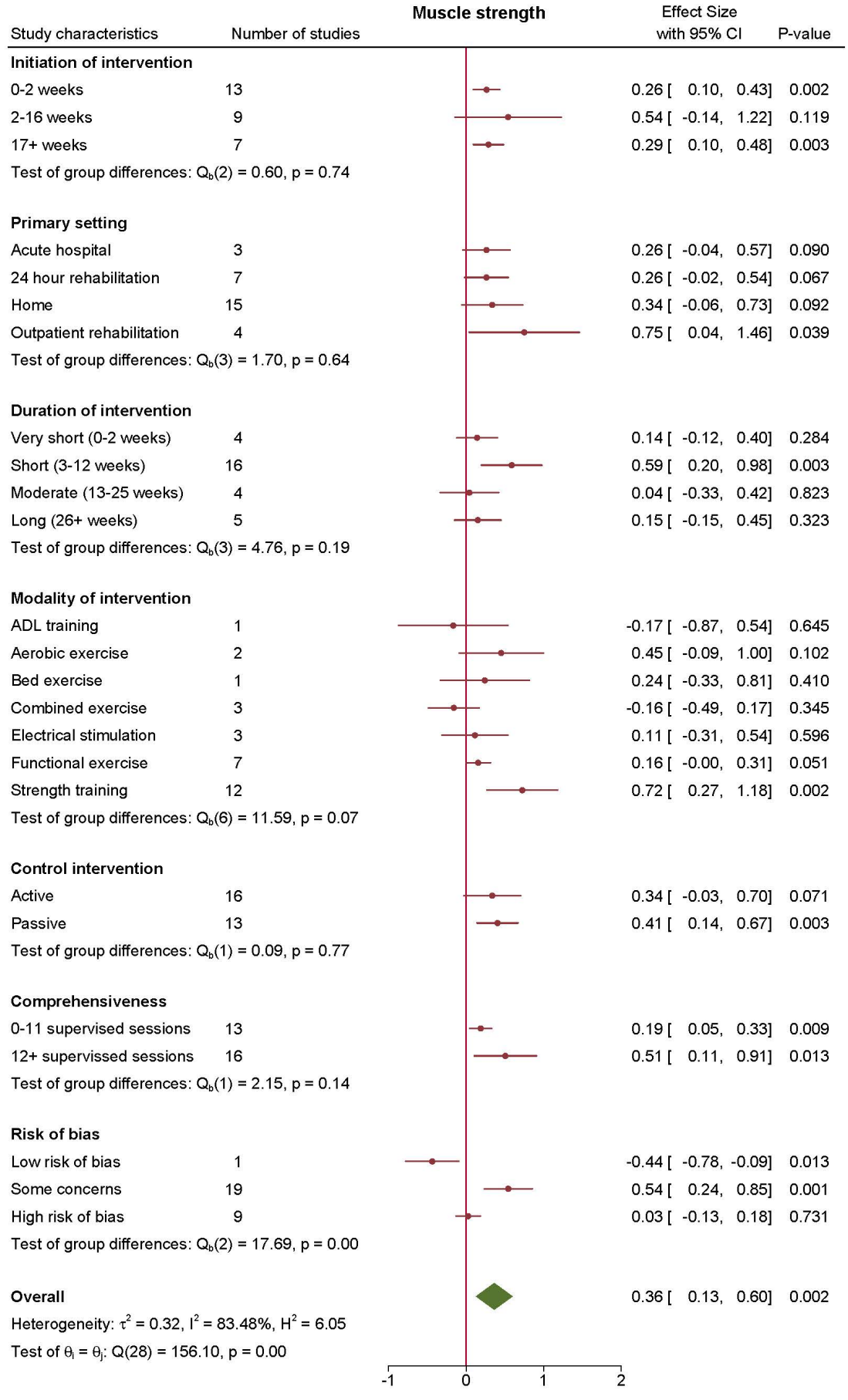


eFigure 8: Forest plot of the effect of exercise therapy on Lower limb muscle strength at short-term.

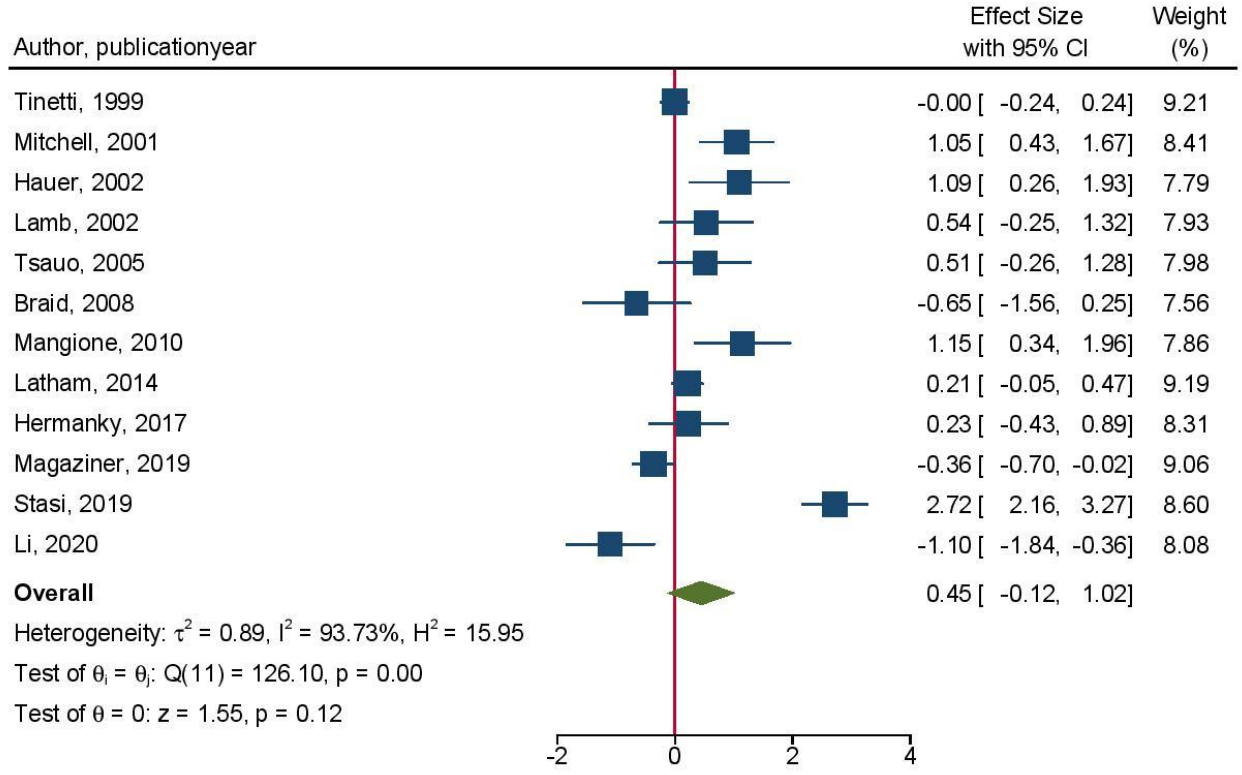


Random-effects REML model

eFigure 9: Subgroup analysis of the effect of exercise therapy on lower limb muscle strength.

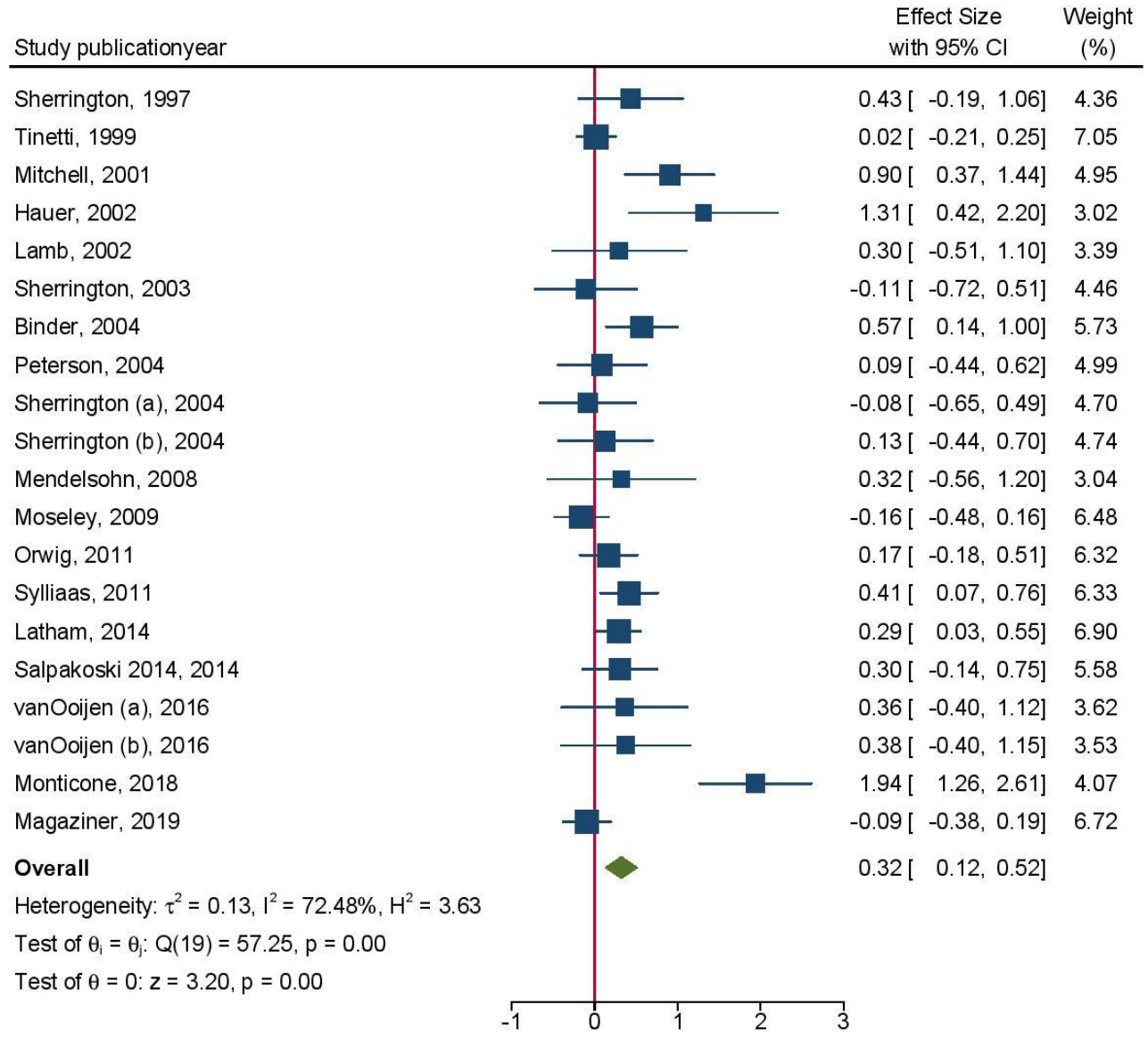


eFigure 10: Forest plot of the effect of exercise therapy on lower limb muscle strength at long-term.



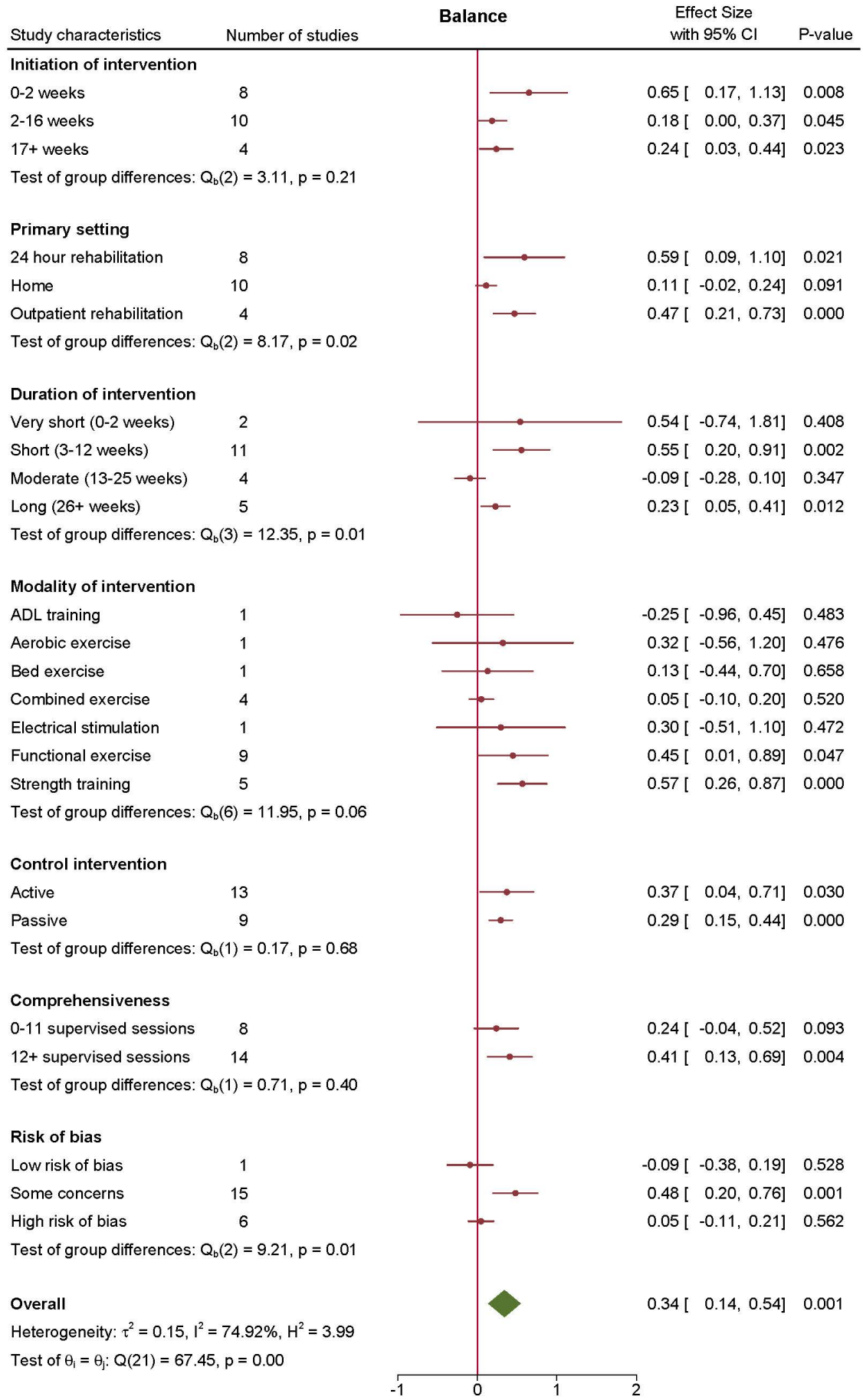
Random-effects REML model

eFigure 11: Forest plot of the effect of exercise therapy on balance at short-term.

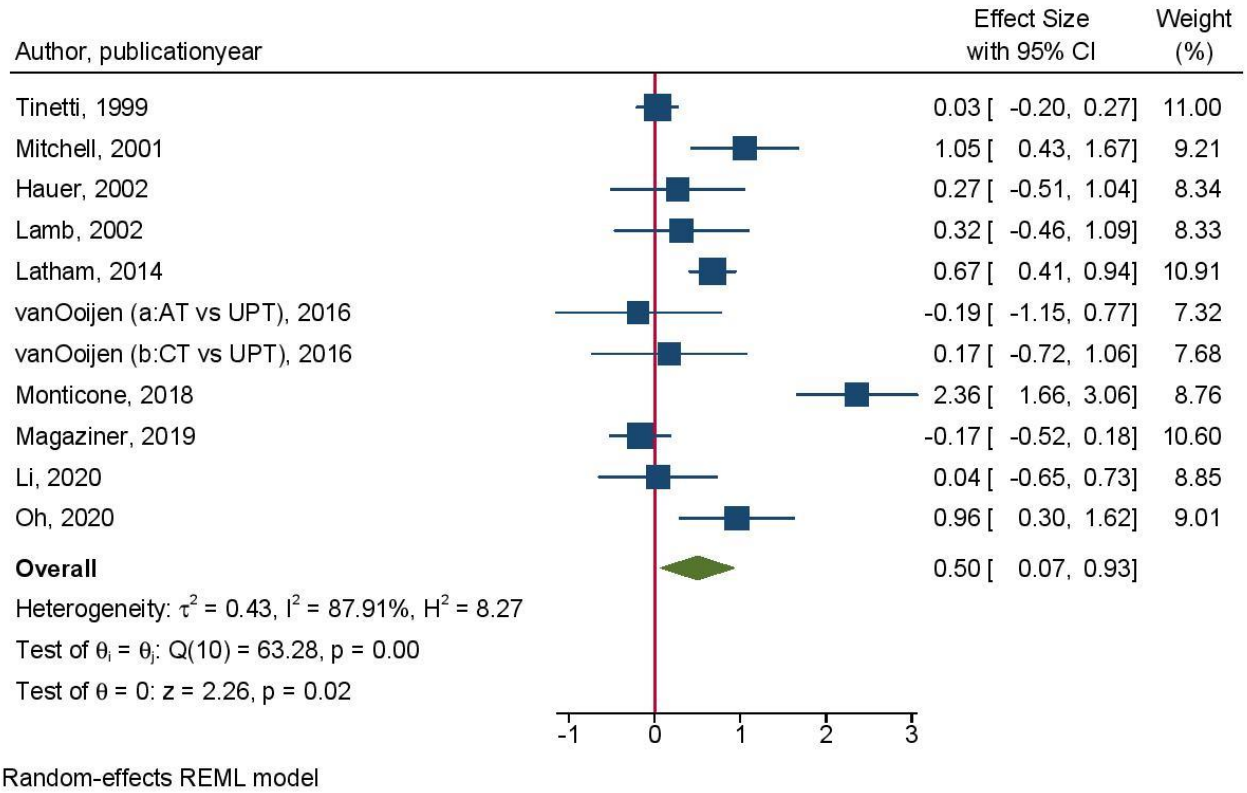


Random-effects REML model

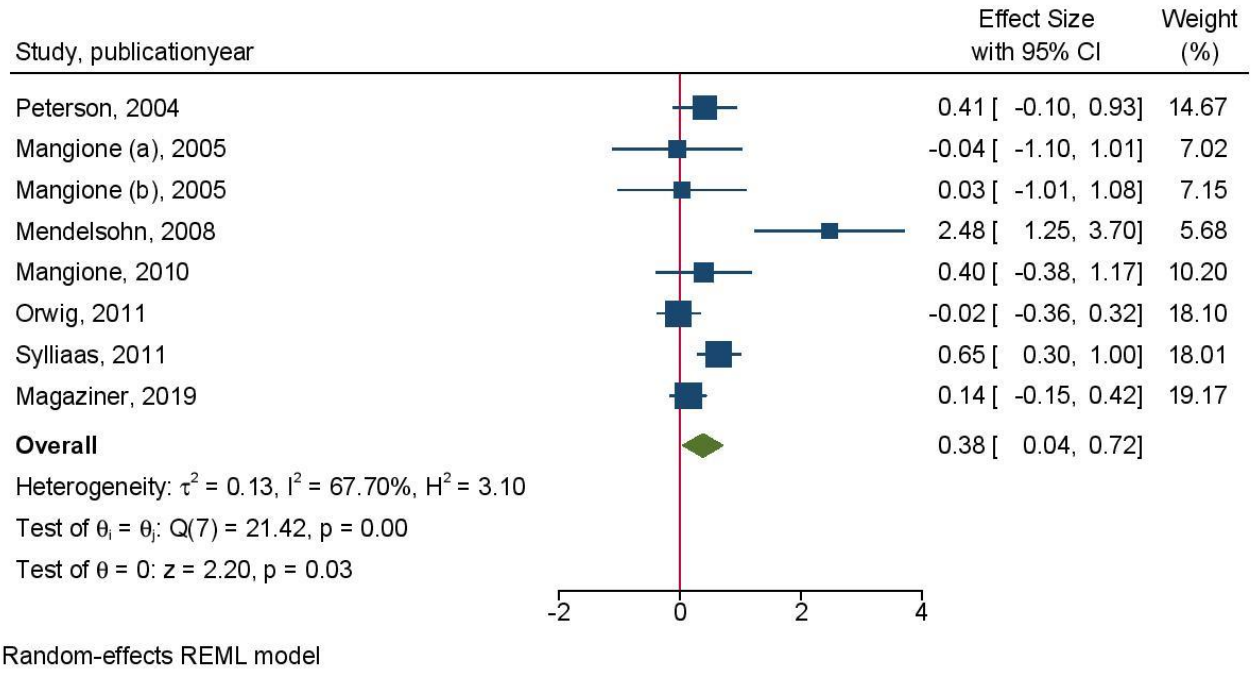
eFigure 12: Subgroup analysis of the effect of exercise therapy on balance.



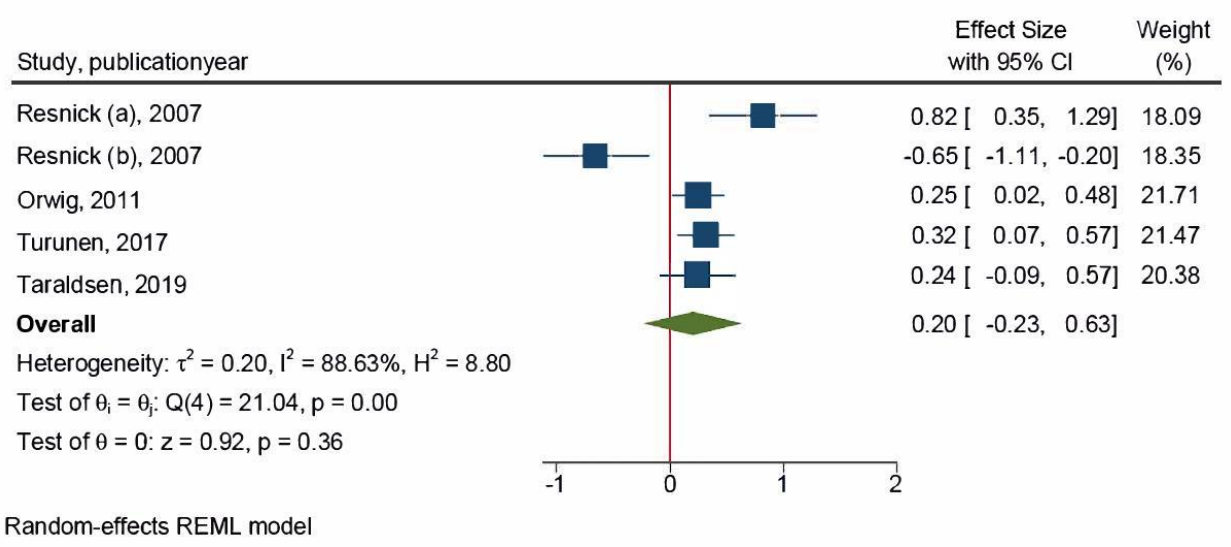
eFigure 13: Forest plot of the effect of exercise therapy on balance at long-term.



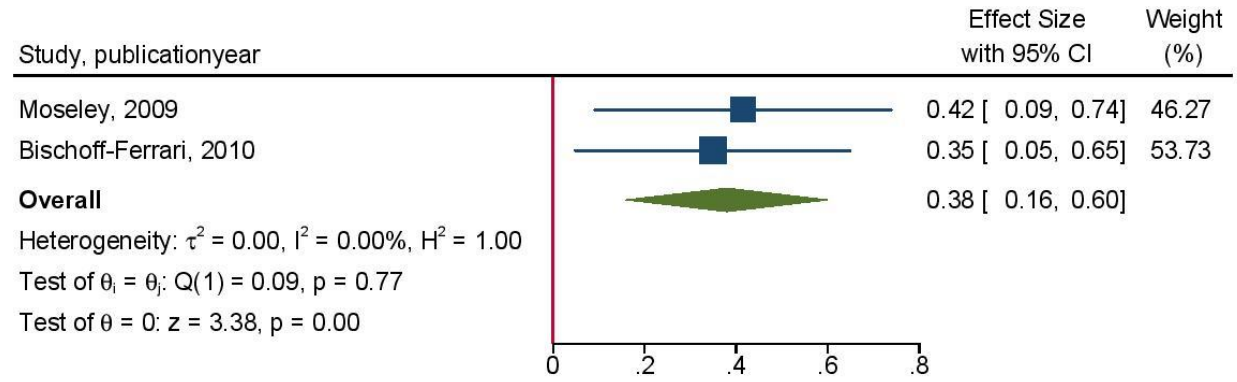
eFigure 14: Forest plot of the effect of exercise therapy on endurance at short-term.



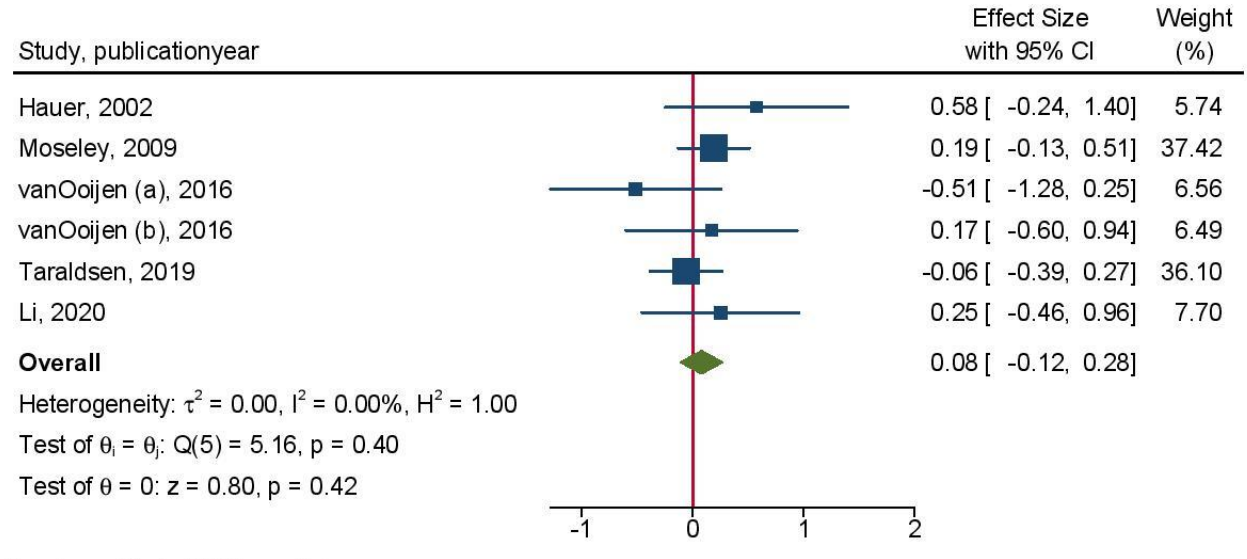
eFigure 15: Forest plot of the effect of exercise therapy on physical activity at short-term.



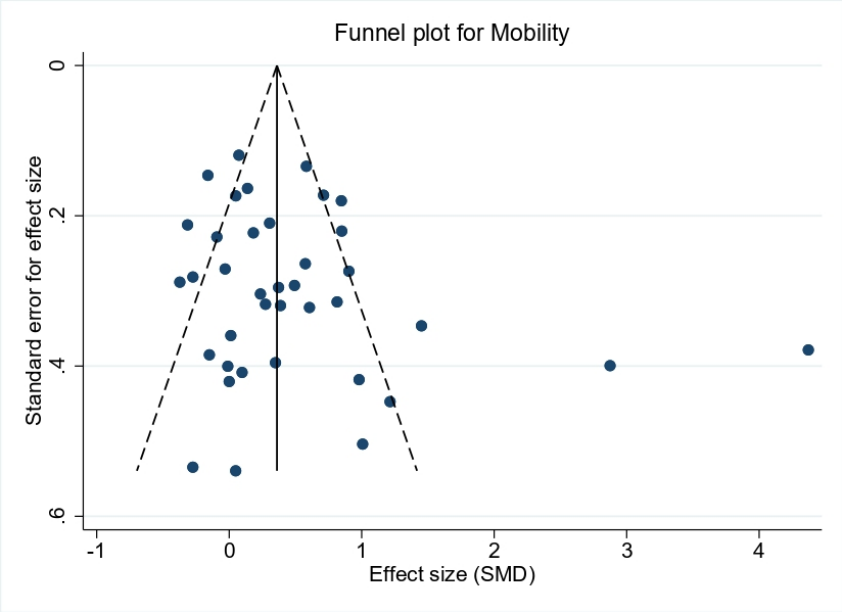
eFigure 16: Forest plot of the effect of exercise therapy on Falls at short-term.



eFigure 17: Forest plot of the effect of exercise therapy on Fear of Falling (FoF) at short-term.

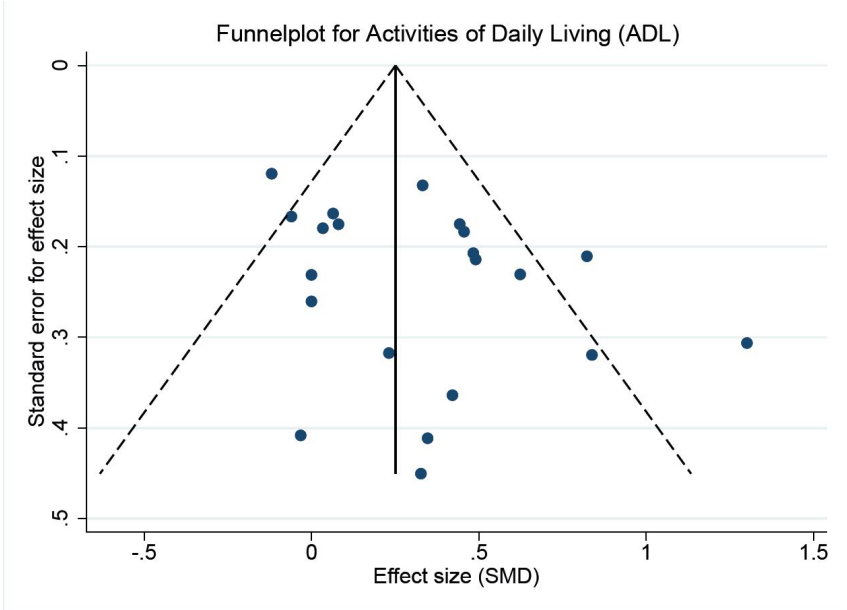


eFigure 18: Funnel plot Mobility



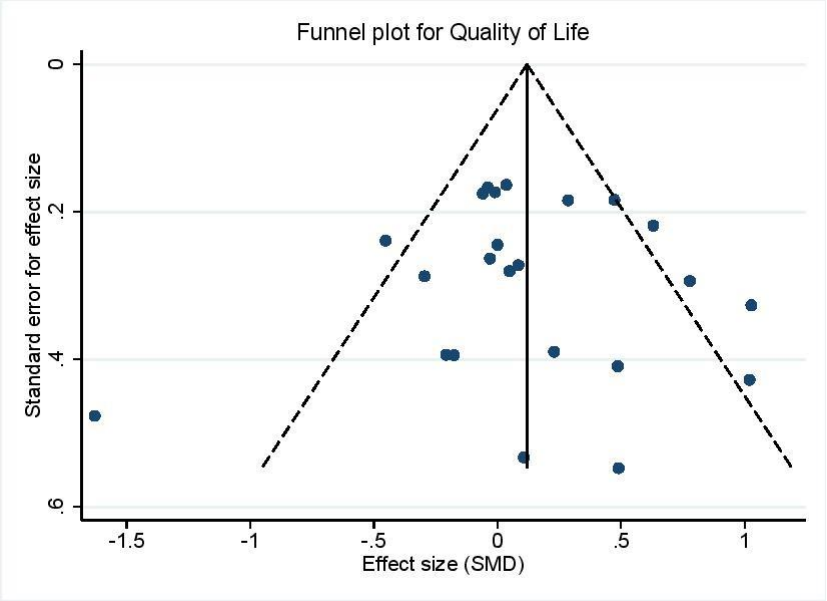
Note: Eggers test for funnel plot asymetry p=0.20

eFigure 19: Funnel plot ADL



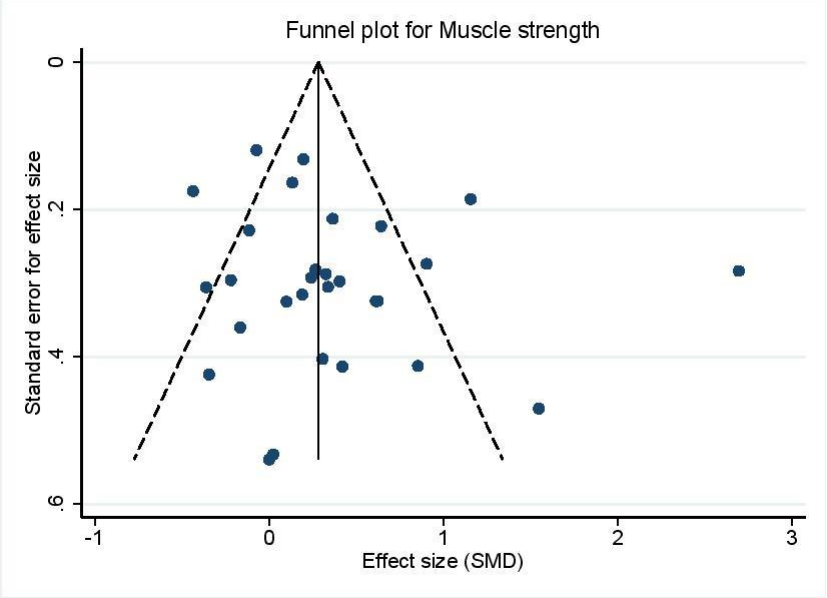
Note: Eggers test for funnel plot asymetry p=0.14

eFigure 20: Funnel plot HRQoL



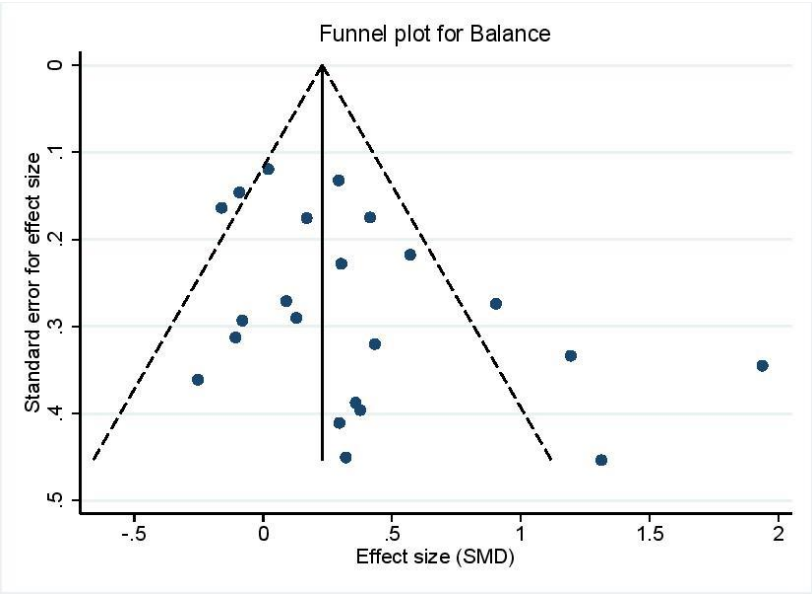
Note: Eggers test for funnel plot asymetry p=0.94

eFigure 21: Funnel plot Lower limb muscle strength



Note: Eggers test for funnel plot asymetry p=0.71

eFigure 22: Funnel plot Balance



Note: Eggers test for funnel plot asymetry p=0.05

Paper 2

Preliminary effect and feasibility of physiotherapy with strength training and protein-rich nutritional supplement in combination with anabolic steroids in cross-continuum rehabilitation of patients with hip fracture: Protocol for a blinded randomized controlled pilot trial (HIP-SAP1 trial).

Hulsbæk S, Ban I, Aasvang TK, Jensen JEB, Kehlet H, Foss NB, Bandholm T, Kristensen MT.

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Trials

STUDY PROTOCOL Open Access

Preliminary effect and feasibility of physiotherapy with strength training and protein-rich nutritional supplement in combination with anabolic steroids in cross-continuum rehabilitation of patients with hip fracture: protocol for a blinded randomized controlled pilot trial (HIP-SAP1 trial)

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Abstract

Background: A 2014 Cochrane review evaluating the effect of anabolic steroids after hip fracture concluded that the quality of the studies was insufficient to draw conclusions on the effects and recommended further high-quality trials in the field. Therefore, the aim of this pilot trial is to determine the preliminary effect and feasibility of a 12-week multimodal intervention consisting of physiotherapy (with strength training), protein-rich nutritional supplement and anabolic steroid on knee-extension muscle strength and function 14 weeks after hip fracture surgery.

Methods: We plan to conduct a randomized, placebo-controlled pilot trial with 48 patients operated for acute hip fracture. The patients are randomized (1:1) to either (1) physiotherapy with protein-rich nutritional supplement plus anabolic steroid or (2) physiotherapy with protein-rich nutritional supplement plus placebo. Outcome assessments will be carried out blinded at baseline (3–10 days after surgery) and at 14 weeks after entering the trial. Primary outcome is the change from baseline to follow-up in maximal isometric knee-extension muscle strength in the fractured limb. Secondary outcomes are physical performance test, patient-reported outcomes, and measures of body composition.

Discussion: If the trial is found feasible and the results show an indication of anabolic steroid being a relevant addition to further enhance the recovery of muscle strength and function in an enhanced recovery after surgery program, this trial will constitute the basis of a larger confirmatory trial.

Trial registration: ClinicalTrials.gov, NCT03545347. Preregistered on 4 June 2018.

Keywords: Hip fracture, Rehabilitation, Physiotherapy, Strength training, Nutritional supplement, Protein, Anabolic steroid

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Background

Sustaining a hip fracture is a common event with major consequences for the individual and society. Northern Europe has the highest incidence rates, led by Denmark, with age-standardized annual rates of 574 per 100,000 in women and 290 per 100,000 in men [1]. Furthermore, incidence rates are expected to increase worldwide due to the aging populations [2].

Patients sustaining a hip fracture experience an immediate loss of knee-extension muscle strength in the fractured limb [3–5]. Decreased lower limb muscle strength is associated with impaired function and disability [4, 6, 7], and it is an independent predictor of falls within 6 months of the hip fracture [8]. As such, a hip fracture often leads to loss of independence, change of residence, further fractures, and high mortality rates [9–13]. Thus, hip fractures pose a substantial economic burden to the health care system and society in general [2, 14, 15].

The evidence regarding rehabilitation following hip fracture shows positive effects on mobility after structured exercise interventions including progressive strength training [16–19]. However, these interventions are mainly started months after the hip fracture has occurred as prolonged programs following ceased standard rehabilitation [16–19]. This is costly and does not reflect the usual standard rehabilitation program offered to patients with hip fracture [20]. On the other hand, although a positive effect of structured exercise has been shown, it seems that these interventions alone are insufficient to overcome the major long-term negative impact of a hip fracture on physical function [10].

A recent (2014) Cochrane systematic review has evaluated the effect of anabolic steroids, either separately or in combination with nutritional supplements, in rehabilitation following hip fracture surgery in terms of functional outcome and adverse events (AEs) [21]. Although positive tendencies were identified in relation to activities of daily living and hip-related function [22, 23], quality of life [22], gait speed [23], and reduction in loss of muscle mass [22, 23], the quality of the studies was insufficient to draw definitive conclusions on the effect [21]. It was emphasized that further high-quality trials are warranted [21], and this is supported by several other narrative reviews in the field [6, 13, 24].

Another common and ongoing challenge to optimal recovery after hip fracture and hospitalization is low protein intake in elderly patients [25]. A recent Cochrane systematic review of the effect of nutritional supplementation for older patients recovering from hip fracture concluded that there might be some effect in relation to reducing complications within the first 12 months, but the evidence is weak [26].

On the basis of our previous early exercise studies [3, 27, 28] and review recommendations [6, 13, 16, 21, 25], it seems rational and strongly needed to apply an early multimodal intervention consisting of muscle-building medicine as well as nutritional and physical exercise treatment in order to enhance short- and long-term outcomes after the disabling event of a hip fracture.

Purpose

The aim of this pilot trial is to investigate the preliminary effect and feasibility of a 12-week multimodal intervention consisting of physiotherapy (functional, balance, and strength training), protein-rich nutritional supplementation, and anabolic steroid (INT) compared with physiotherapy (functional, balance, and strength training), protein-rich nutritional supplement, and placebo (CON) in rehabilitation following hip fracture surgery on fractured limb knee-extension muscle strength at 14-week follow-up.

We hypothesize the following:

1. An intervention consisting of physiotherapy, nutritional supplementation, and anabolic steroid is a feasible and preliminary safe treatment in elderly patients with hip fracture when initiated in the acute orthopedic ward and continued for 12 weeks.
2. This multimodal intervention (physiotherapy, nutritional supplementation, and anabolic steroid) is more efficacious in improving muscle strength and physical function 14 weeks after hip fracture surgery than physiotherapy, nutritional supplementation, and placebo.

Methods

Trial design

The HIP-SAP1 trial (Hip fracture, Strength training, Anabolic steroid and Protein) is a randomized, blinded, single-center, placebo-controlled, two-arm, parallel-group, superiority pilot trial. We intend to include 48 patients with hip fracture who will be randomized (1:1) to one of two arms.

This clinical trial protocol is based on the PREPARE trial guide [29], the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Additional file 1), and the CONSORT (Consolidated Standards of Reporting Trials) checklist (extension to randomized pilot and feasibility trials). The Template for Intervention Description and Replication (TIDieR) checklist [30] is used for description of the intervention. The trial was registered at ClinicalTrials.gov (identifier NCT03545347) before the first participant was included. The trial will be conducted at Copenhagen University Hospital Hvidovre in cooperation with all municipalities in the catchment area of the hospital.

Recruitment

Patients admitted to the Hip Fracture Unit at the Orthopedic Department of Copenhagen University Hospital Hvidovre will be screened for eligibility (see inclusion and exclusion criteria in Table 1). The sampling method is consecutive, though screening and inclusion will be discontinued during trial staff's absence. A screening log will be kept. Annually, approximately 475 patients above 60 years of age are operated at the Hip Fracture Unit. We assume that 20% would be excluded due to nursing home residency, another 20% would be excluded due to cognitive impairments, and the remaining criteria would account for approximately 25% exclusions. That would leave us with 14 eligible patients per month. We aimed at completion of recruitment within 1 year, but because recruitment has been lower than expected, the recruitment period has been extended to September 2020.

Table 1 Inclusion/exclusion criteria

Inclusion criteria

- Patients who have undergone surgery for a hip fracture at Amager-Hvidovre University Hospital and admitted to the Hip Fracture Unit at the hospital
- Age ≥ 60 years
- Ability to speak and understand Danish and having a Danish Social Security number
- Able to give written informed consent
- Residing at home and with an independent prefracture indoor walking ability (New Mobility Score ≥ 2)

Exclusion criteria

- Postoperative weight-bearing restrictions
- Multiple fractures
- Active cancer or suspected pathological fracture
- Patient unable/unwilling to cooperate for testing and rehabilitation
- Planned/elective hospitalization within the trial period
- Cognitive dysfunction determined by chart review, reported by nursing staff, or observed by trained research staff (disoriented, dementia, active delirium)
- Uncontrolled blood pressure (systolic > 150 mmHg or diastolic > 100 mmHg)
- Heart disease in the form of peri-, myo-, or endocarditis
- History of stroke with motor disability
- Heart failure (New York Heart Association class III and IV)
- Evidence of kidney failure or renal impairment (estimated glomerular filtration rate < 30 ml/min/1.73 m^2 or serum creatinine > 200 μmol/L)
- Abnormal liver function tests (alanine aminotransferase, γ-glutamyltransferase, bilirubin, or alkaline phosphatase > 2 times the upper limit of normal) or history of hepatic tumor
- Elevated hematocrit ≥ 50%
- History of breast or prostate cancer
- Abnormally elevated serum prostate-specific antigen (PSA) assessed at the 3-week control* corresponding to PSA < 4.0 μg/L (60–70 years), PSA < 5.0 μg/L (> 70 years)
- Allergic to any ingredient in the Deca-Durabolin solution (nandrolone, benzyl alcohol, arachis oil [peanut oil], and allergy to peanuts or soya) or milk protein allergy (related to the nutritional drink)

*PSA during admission could be increased due to catheterization; therefore, PSA will be assessed at 3 weeks, and patients will be excluded at this time point if elevated values are identified

Information regarding inclusion and exclusion criteria will be obtained through medical records and by asking the patient or relatives. Assessment of eligibility is a two-stepped process because hematocrit and liver functions tests are not standard tests following hip fracture surgery, and therefore blood tests cannot be taken until after informed consent has been obtained.

The initial screening for eligibility will be conducted by the project coordinator, and final assessment of patients eligible for inclusion in the trial will be conducted by the principal investigator or two other medical doctors allocated to the hip fracture unit and trained in the protocol. These individuals will all be blinded to the allocation sequence.

Eligible patients will be addressed at the ward by the project coordinator 1–4 days following surgery. Patients will receive full oral and written information from the project coordinator about the purpose of the trial, process, and potential benefits and risks. The information is delivered by the project coordinator in simple language without technical or value-laden terms, and it is given in a considerate manner, tailored to the individual subject. The patients will be offered 24 h to consider participation, and they will be informed of the possibility of having a relative or other person accompanying them for further information. It is ensured that all questions the patient might have are answered. Patients who agree to participate must sign an informed consent form, which the project coordinator also signs for the given information.

Patients will be informed that participation is voluntary and that they can withdraw their consent at any time and leave the trial. It is emphasized that nonparticipation will not affect further treatment at the department.

Intervention

After inclusion in the trial, baseline assessments will be performed, and hereafter patients will be randomized (1:1) to one of two arms receiving either (1) physiotherapy with nutritional supplementation and anabolic steroid (INT) or (2) physiotherapy with nutritional supplementation and placebo (CON). See Fig. 1 for a flowchart of the trial.

Trial medication

Nandrolone is a synthetic anabolic-androgenic steroid; it is protein-building, promotes mineralization of bones, and stimulates the formation of red blood cells. Nandrolone is structurally related to naturally occurring testosterone, but it shows enhanced anabolic effect and a reduced androgenic effect. Nandrolone is used medically

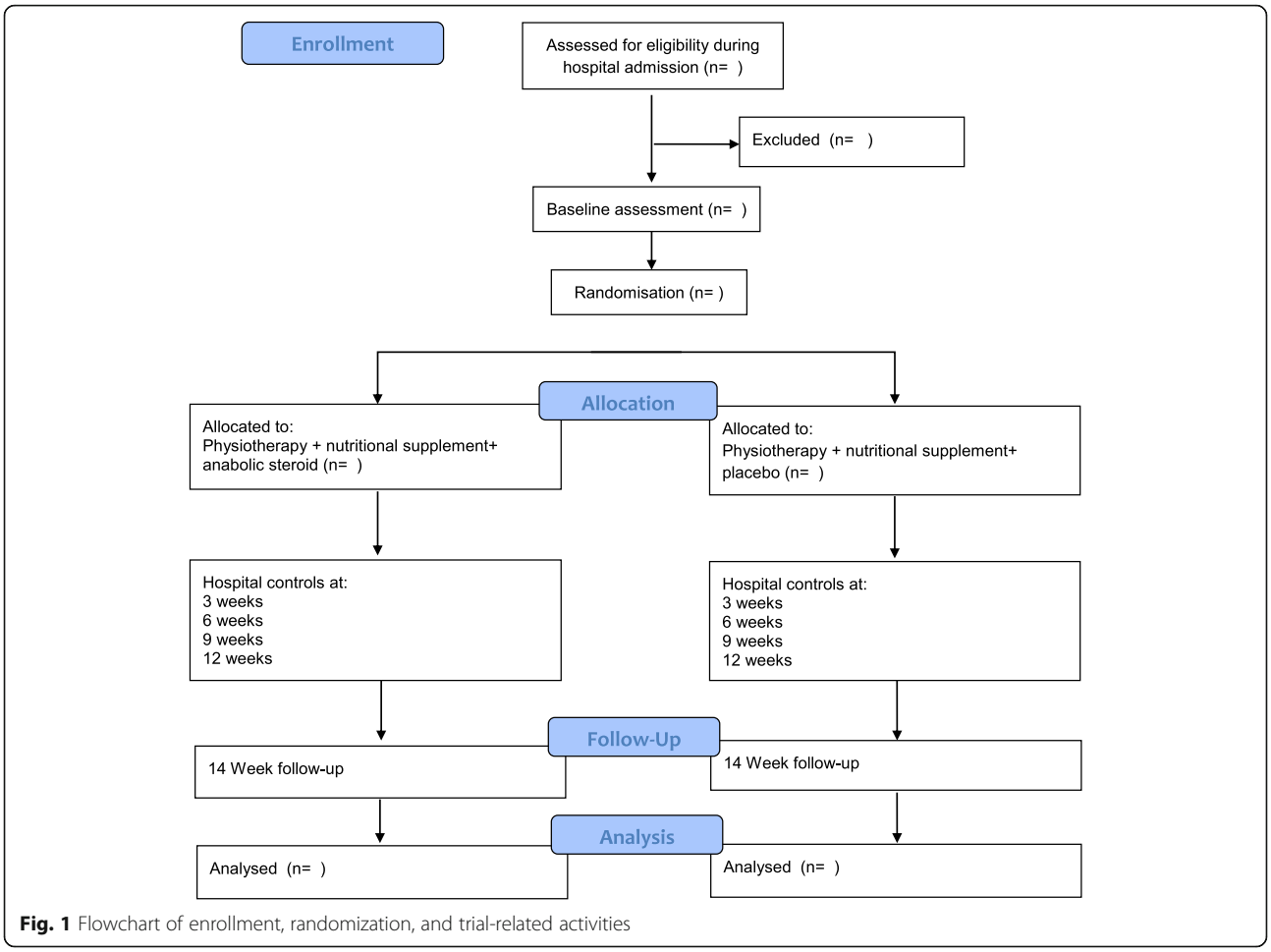

Fig. 1 Flowchart of enrollment, randomization, and trial-related activities

in the form of esters (nandrolone decanoate) and is intended for use in osteoporosis in postmenopausal women and for some types of anemia. Deca-Durabolin is an intramuscularly administered depot preparation of nandrolone decanoate.

- *Active arm (INT)*: Patients will receive intramuscular injections of nandrolone decanoate (Deca-Durabolin 50 mg/ml; Aspen, Durban, South Africa) every 3 weeks. The first injection will be administered at baseline and the last injection at week 12. The solution is injected into the gluteal muscle or rectus femoris. The dosage varies, dependent on gender and testosterone level (men). Women will receive 50 mg, men with total testosterone ≥ 11 nmol/L will receive 100 mg, and men with total testosterone < 11 nmol/L will receive a dose of 200 mg. The cut of 11 nmol/L for total testosterone is determined on the basis of the age-related reference interval (men 50–70 years, 8.4–25.4 nmol/L) and lies below the mean value of 14.6 nmol/L (24).
- *Placebo arm (CON)*: Patients will receive a placebo injection of 1 ml of sodium chloride 9 mg/ml (produced by Fresenius Kabi, Bad Homburg, Germany), following the same intervals as for the active agent. The fluid is injected intramuscularly, and the product has no therapeutic effect.

Nutritional supplementation

Patients in both arms will receive two daily nutritional drinks while under hospital admission, which is already a standard procedure at the unit. At discharge, patients will receive nutritional drinks covering the following 3 weeks. At every control visit at the hospital, additional drinks will be provided covering the next 3 weeks.

The protein-rich nutritional supplement is planned to account for at least 35% of the patient's daily protein requirement. The recommendations for geriatric patients with acute disease is 1.2–1.5 g/kg body weight/day [31]. The standard used at the hip fracture unit is 1.35 g/kg body weight/day; this value will be used to calculate the protein supplementation throughout the study. The protein-rich nutritional supplement is a liquid containing 18 g of milk-based protein per bottle (RESOURCE 2.0 + fiber; Nestlé Health Science, Sydney, Australia). On the basis of the standard used in this study, dependent

on their body weight, most patients will receive two bottles per day for 12 weeks.

Physiotherapy

Patients will receive physiotherapy as part of the department's standard procedure, starting on the day after surgery and continued daily until day 3 postoperatively, and thereafter continued on weekdays. The standard physiotherapy treatment includes functional exercises, such as transfers and walking, and exercise therapy primarily aimed at lower extremities. An exercise guideline with 12 specific exercises focusing on joint movement, lower limb muscle activation, and edema prophylaxis will be handed out and progressed individually [3]. After baseline testing and randomization, knee-extension strength training using weight cuffs will be added. The intervention is adjusted to meet the abilities of the individual patient, considering their medical and prefracture status. On days of baseline testing, the testing replaces the normal physiotherapy intervention.

After discharge, patients will receive physiotherapy in the municipality, which is already a standard procedure in Denmark following a hip fracture. The patients will receive physiotherapy 1 h twice weekly up to and including the 12th week after inclusion in the study. The physiotherapy intervention in the municipality will typically be a group intervention, and it will be based on the patient's individual level. The training will consist of a warmup (aerobic exercises such as cycling), functional training (e.g., walking exercises, climbing stairs, sit-to-stand exercise), balance training (with different degrees of support and different types of underlay), and lower limb exercises (e.g., using elastic bands and progressive strength training). In regard to strength training, two exercises will be obligatory (knee extension performed as unilateral and bilateral leg press), which will be performed according to a standardized protocol (Additional file 2). Patients will perform three sets for each exercise. During the first 2 weeks, the exercises will be performed with approximately 15 repetitions (reps) and an intensity of 15 repetition maximum (RM), and thereafter 2 weeks of 12 reps with 12 RM, and for the remaining 8 weeks 10 reps with 10 RM [28]. The physiotherapist will log the load, repetitions, and pain for each set during the session and progress the load on a set-to-set basis. The patient is instructed to take as many repetitions as possible in each set; if the number of repetitions varies by more than 3 in relation to the number planned, then the load will be adjusted. Both concentric and eccentric phases are performed slowly and in a controlled manner (see Additional file 2 for exercise log).

The engaged physiotherapists in the municipalities are experienced and have been involved in the process of designing/describing the physiotherapy intervention. Prior to initiating the trial, the primary author visited the sites to ensure consistency across the nine rehabilitation centers.

General trial treatment procedures

Patients included in the trial will be treated according to the department's standard procedures for surgery, anesthesia, and perioperative care. Type of operation is determined by a well-defined algorithm based on the type of fracture [32]. Standard perioperative care includes D vitamin and calcium supplementation dependent on the patient's individual level. Further, a standardized liberal transfusion protocol is used with transfusion if hemoglobin (Hb) is < 9.7 g/dl.

After enrollment, patients will be assessed in regard to the study's primary and secondary outcomes. Thereafter patients are randomized, and the first injection of the trial solution is administered by the dedicated nurse. In case of the primary nurse being absent, a second nurse trained in the protocol will substitute for her.

After discharge, the patient will receive weekly telephone calls from the project coordinator in order to ensure and monitor compliance. The patient will be asked about the amount of consumed nutritional supplement and attendance at physiotherapy sessions. Further, the patient will be asked about their well-being in order to detect potential side effects of the intervention. An interview guide will be used to assure systematic collection of information.

Every 3 weeks, the patient will attend a control visit at the hospital. The dedicated nurse will carry out blood tests and inject the treatment solution according to randomization group. Compliance with the trial as well as outcome/safety parameters will be monitored. Further, the nutritional supplement covering the following 3 weeks will be handed out at the visit.

The intervention period for the nutritional supplementation and exercise intervention is 12 weeks. The patient will receive the last injection at week 12. Further, at the 12-week appointment, an activity monitor will be applied to the patient's thigh (activPAL; PAL Technologies, Glasgow, UK), which will monitor activity the following week.

Follow-up will occur during week 14, when patients will be assessed according to the primary and secondary outcomes. To ensure that all potential side effects are detected, one last telephone call is conducted during week 16, and thereafter the patient will have no further obligations in relation to the trial. See Fig. 1 for the flow of enrollment and trial-related events.

Criteria for discontinuation

Safety parameters are listed under the "Secondary outcomes" heading and will be observed throughout the study. If values of hematocrit, liver tests, and prostate-specific antigen (PSA) exceed the safety thresholds, the

treatment with Deca-Durabolin will be discontinued. Further, if women experience androgenic side effects, treatment will be discontinued. Regarding the remaining safety parameters, where no safety threshold is specified, values outside the reference interval will be evaluated by the medical doctors trained in the protocol and relevant action will be taken if necessary.

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the trial at any time for any reason. Further, the investigator has the right to withdraw a patient from the trial at any time if a withdrawal is considered in the best interest of the patient.

Patients who have ceased intervention prior to its determination will be asked to follow the scheduled controls, and data will be collected according to the protocol. Patients who choose to withdraw from the trial will be asked the reason why. However, it is emphasized that the patient is not obliged to state the cause. If a patient drops out and is unwilling to follow the protocol, permission will be asked to continue weekly phone calls to monitor potential side effects (for 4 weeks after last injection). Further, the patient will follow standard treatment for hip fracture and see the orthopedic surgeon at the regular postoperative visit.

Outcome

Outcomes will be assessed blinded at baseline and at 14 weeks after entering the trial. Safety parameters will be assessed at baseline and 3, 6, 9, 12, and 14 weeks after inclusion. Outcome assessment is carried out primarily by the project coordinator, who is an educated physiotherapist with 13 years of practical experience in orthopedics. In the project coordinator's absence, an experienced physiotherapist trained in the protocol will conduct the assessments. In the text below, outcome parameters and time of assessment are specified, which are illustrated in Fig. 2.

The baseline assessment might extend over 2 days in order to avoid patient exhaustion, and it will be conducted during the time period from postoperative day 3 until postoperative day 10. The follow-up assessment is conducted during week 14 from time of randomization (± 7 days from time of randomization). The control every 3 weeks is conducted within 3, 6, 9, and 12 weeks (± 7 days from time of randomization).

Primary outcome

- Change in maximal isometric knee-extension strength (N·m/kg) in the fractured limb (maximal voluntary torque per kilogram body mass) from baseline to the 14-week follow-up. Knee-extensor strength is chosen as the primary outcome because it is closely related to the exposure (strength training), which is what we want in this pilot trial. Hence, we consider the outcome a surrogate outcome measure for a more clinically meaningful one, such as mobility. Pertaining to this, knee-extensor strength is associated with impaired mobility [4, 33]. Knee-extensor strength is measured using a belt-fixed handheld dynamometer (Commander Muscle Tester; JTECH Medical, Midvale, UT, USA) [3, 27, 28]. The test is conducted as described by Kronborg et al. [3] with the patient seated on the bedside, with hips and knee joint angle in 90-degree flexion and hands placed on the mattress for support. The lever arm length is measured by tape measure between the lateral epicondyle of the femur and the center of the dynamometer transducer pad placed 4 cm above the lateral malleolus of the tibial bone. Four trials must be completed, and the highest obtained value in Newtons (N) will be used for analysis. Tests are performed with standardized verbal encouragement. The isometric knee-extension strength is expressed in N·m/kg, which is derived from the units of force measured in Newtons (N) multiplied by the corresponding lever arm measured in meters (m), divided by the weight of the patient in kilograms (kg).

Secondary outcomes

The following outcomes will be compared between the two groups. Unless stated otherwise, the change in values are measured from baseline until 14 weeks. Figure 2 illustrates time points for assessment of each outcome.

- Maximal isometric knee-extension strength (N·m/kg) in the fractured limb as a percentage of the nonfractured limb. Description of the measurement method is provided under the "Primary outcome" heading.
- Maximal isometric knee-extension strength (N·m/kg) in the nonfractured limb. Description of the measurement method is provided under the "Primary outcome" heading.
- Hand-grip strength in the dominant hand measured using a digital handheld dynamometer (Saehan Grip, DHD-1; Saehan, Changwon, Korea). Hand-grip strength will be expressed in kilograms. A standardized test protocol will be used similar to the one described by Bodilsen et al. [34].
- Fat mass (total body weight) assessed by dual x-ray absorptiometry (DEXA), expressed in kilograms. DEXA is performed as a whole-body scan and is conducted in accordance with the department's standard procedures.

	Study period						
	Pre allo-cation	**Allo-cation**	**Post-allocation**				**Follow-up**
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5
	Enroll-ment	**Base-line**	*3 weeks*	*6 weeks*	*9 weeks*	*12 weeks*	*14 weeks*
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTION							
Deca-Durabolin		X	X	X	X	X	
Placebo		X	X	X	X	X	
ASSESSMENTS							
Isometric knee-extension strength		X					X
Hand Grip Strength		X					X
Fat mass		X					X
BMD (Bone mineral density)		X					X
LBM (Lean body mass)		X					X
Mini Nutritional Assessment (MNA)		X					X
10-meter fast walk		X					X
Timed Up & Go test		X					X
De Morton Mobility Index (DEMMI)		X					X
Physical activity (Upright time), ActivePAL						X	
New Mobility Score (NMS)		X*	X	X	X	X	X
Health-related quality of life, EQ-5D-3L		X*					X
Hip fracture-related pain, Verbal Rating Scale		X	X	X	X	X	X
Global Rating of Change (GRoC) -walking			X	X	X	X	X
Short Falls Efficacy Scale-I		X					X
Fatigue, SF36 vitality subscale		X*	X	X	X	X	X
Geriatric Depression Scale (GDS)		X*					X
Re-admissions							X
Residential status (and home care)		X*					X
Mortality							X
Total testosterone		X					X
Luteinizing hormone (LH), Follicle-stimulating hormone (FSH)		X					X
Sex hormone binding globulin (SHBG)		X					X
Lipid profile		X					X
C-reactive protein (CRP)		X					X
Safety Parameters		X	X	X	X	X	X

*Assessment takes place at baseline but refers to the time-period prior to the fracture.

Fig. 2 Schedule for enrollment, intervention, and outcome assessments (SPIRIT)

- Bone mineral density (BMD) assessed by DEXA. Registration of total body, total hip, femoral neck, and lumbar spine BMD. Expressed in g/cm^2. Further T-score is registered. The scan is performed as a whole-body scan and is conducted in accordance with the department's standard procedures.
- Lean body mass assessed by DEXA and expressed in kilograms. Registration of total body, legs bilaterally, and arms bilaterally. The scan is performed as a whole-body scan and is conducted in accordance with the department's standard procedures.
- Nutritional screening using the Mini Nutritional Assessment–Short Form (MNA-SF). Total score from 0 to 14 points, high scores indicating better nutritional status. The score is frequently used for assessing nutritional status in patients with hip fracture and predicts mortality and readmissions [35, 36].
- Gait speed is assessed using the 10-m fast speed walking test, standing start. A standardized test protocol is used, and the best result of three trials is reported in meters walked per second (m/s) [28].
- The Timed Up & Go Test is performed using a four-wheeled rollator and measured in seconds. The patient has to rise from a chair, walk 3 m, turn around, walk back, and sit down [37]. A standardized instruction will be used [38].
- The de Morton Mobility Index is used for measuring mobility and consists of 15 mobility items ranging from mobility in bed to dynamic balance. The test result is a total score from 0 to 100, with 100 representing the highest level of mobility [39–41].
- Activity: Sedentary time (lying/sitting), upright time (standing/walking), steps, and transfers is measured using a body-worn accelerometer-based activity monitor (activPAL) [42]. The monitor will be attached to the thigh. The patient will wear the monitor for 1 week from the time point of the 12-week control.
- Functional level is assessed by the modified New Mobility Score [43–45]. The patients are interviewed about walking ability indoors, outdoors, and when shopping. At baseline, the score refers to the week prior to hospital admission. The total score ranges from 0 to 9. A higher score indicates greater independence.
- EQ-5D-3L is used for assessing health-related quality of life [46–48] and is administered via interview. At baseline assessment, the score refers to the time prior to the fracture.
- Hip fracture-related pain at rest and during outcome assessment is evaluated using the Verbal Rating Scale [49]. The patient is asked to rate the intensity of pain in relation to five adjectives: "no pain," "slight pain," "moderate pain," "severe pain," and "unbearable pain." The answer is converted to a number between 0 and 4 on an ordinal scale.
- A global rating of change scale will be used for assessment of patient-perceived change in walking ability during the trial period. Patients will be asked one question related to change in mobility and have five response options ranging from much better to much worse.
- The Short Falls Efficacy Scale–International is used to measure the patient's fear of falling (score range from 7 to 28, with higher scores indicating a greater fear of falling) [50, 51]. It is administered as an interview.
- Fatigue is assessed using the SF-36 (36-item Short Form Health Survey) vitality subscale, consisting of four items related to fatigue/energy [52, 53]. Scores range from 0 to 100 points; high score defines a more favorable health state. Administered as an interview. The baseline assessment refers to the time prior to the fracture.
- Depression is assessed using the Geriatric Depression Scale, which is administered as an interview [54, 55]. Score range, 0–15. Baseline assessment refers to the time prior to the fracture.
- Readmissions within 14 weeks will be assessed through the medical journal.
- Residential status, including home care, will be recorded by interview or medical journal.
- Mortality will be assessed through the medical journal/Danish civil register.

Blood tests

All blood tests are conducted in accordance with the department's standard procedures.

- Total testosterone (nmol/L), luteinizing hormone (IU/L), follicle-stimulating hormone, (IU/L), and sex hormone-binding globulin (nmol/L).
- Lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride) (mmol/L).
- C-reactive protein (mg/L).

Safety parameters

The following values are assessed: hemoglobin, hematocrit, creatinine, carbamide, sodium (Na^+), potassium (K^+), calcium, international normalized ratio (INR), liver tests, PSA, and glucose.

For the following parameters, safety thresholds are defined: hematocrit (safety threshold, values > 0.50), liver tests (albumin, alanine aminotransferase, γ-glutamyltransferase, bilirubin) (safety threshold, liver test values > 3 times the upper limit of normal), and PSA (safety threshold, increase to > 50%).

Other safety parameters are blood pressure (assessed using a digital blood pressure monitor, measured in mmHg) and facial hirsutism (assessed using the two face-related items of the modified Ferriman-Galwey hirsutism score, 0–8 points) [56], hoarseness (assessed through weekly interviews and hospital controls every 3 weeks), edema (assessed through weekly interviews and hospital controls every 3 weeks), and falls (a question regarding falls will be part of an interview guide used for the weekly telephone calls). Other AEs/adverse reactions (ARs) will be assessed through weekly interviews and hospital controls every 3 weeks.

Feasibility outcomes

Feasibility will be assed according to the following aspects: number of eligible patients, inclusion rate per month, feasibility and suitability of outcome measures, acceptability of the treatments to the patients, adherence to the treatment, retention to the scheduled controls and follow-up, and number and severity of AEs.

Sample size

The sample size is determined on the basis of the primary outcome (change in knee-extension strength of the fractured limb) and calculated to detect a between-group difference in the change score of 0.2 N·m/kg in favor of the intervention group using Lehr's formula with an SD of 0.22 N·m/kg. The difference in change scores of 0.2 N·m/kg is defined by the authors, and it is a larger difference than what could be considered the minimal clinically important difference. Because we only wish to explore the potential of effect in this pilot trial [57], and not establish effect, we argue that it is acceptable. The SD of 0.22 N·m/kg is obtained from a previous study [3]. Hence, we acknowledge that if this trial shows feasibility and preliminary effect of the intervention, confirmatory effect will need to be demonstrated in at least one phase III-like confirmatory trial. On the basis of this estimate, 20 patients are needed in each group using a standard of 80% power and type I error rate of 5%. Forty-eight patients are therefore planned for inclusion in the present trial to allow for an expected dropout rate of 20%. In case of dropout, new patients will be enrolled in the trial to ensure a minimum of 20 patients in each group who have completed the intervention.

Randomization and allocation

The patients will be randomly assigned to one of the two groups by a 1:1 allocation ratio. Block randomization (blocks of 2 and 4) will be used, and patients will be stratified for type of fracture (cervical femoral versus trochanteric hip fracture) and sex. The allocation sequence is computer-generated (random number generator) by a qualified person not involved in the trial. The allocation sequence is retained in a locked cabinet by the person generating the sequence. To ensure allocation sequence concealment, sequentially numbered, opaque, sealed envelopes are used. When a person is included in the trial, the coded envelope is broken by the nurse injecting the trial medication. The envelopes contain information on allocation and a registration form used for medicine accounting. The envelopes will be retained by the nurse injecting the medication and kept in the nurse's office, which is geographically separated from the hip fracture unit and the Department of Physiotherapy.

Information about allocation will not be revealed before all data analysis has been performed.

Blinding procedure

The patients, healthcare providers, intervention deliverers, data collectors, and outcome assessors are all blinded to whether the patient has received trial medication or placebo. The only person not blinded is the nurse drawing the envelope and injecting the medication/placebo, but she has no other involvement in the trial. The nurse is instructed not to reveal to the patients to which intervention they are allocated. No effort will be made to blind the research hypotheses from the participants.

Blinding for the individual patient will be broken only in cases where the continued treatment of the patient requires knowledge of allocation. Twenty-four-hour access to unblinding is assured. If the code is broken, date and reason will be registered, and the envelope will be signed by the investigator.

Data collection and management

For each patient included in the trial, an electronic case report form (CRF) will be completed in a browser-based database, Research Electronic Data Capture (REDCap). Data entered via REDCap will be stored via an encrypted connection and will meet the applicable requirements for data security. The REDCap option of validating the entered data will be used to promote the quality of data. Correction of data will be visible and accessible through REDCap's audit trail. The audit trail will be saved equivalent to trial data. The trial data will be saved for at least 5 years as required by the Danish Data Protection Agency (journal no. AHH-2017-090, I-Suite no. 05980). The principal investigator and sponsor are responsible for managing and archiving data in accordance with the relevant legislation, including the Act on Processing of Personal Data and Health Act.

Data monitoring

The trial will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

principles of good clinical practice (GCP). The project is registered with EudraCT (identifier 2017-001543-13) and is monitored by the independent GCP unit at Copenhagen University Hospital Bispebjerg. The GCP unit will monitor the project throughout the trial and assure that the trial is executed, registered, and reported according to the protocol, written standard operating procedures, GCP, and Danish legislation. Scheduled monitoring visits will be conducted throughout the trial. The first initiating visit is prior to commencement of the trial. The focus of the following visit is on monitoring the trial master file, protocol compliance, data quality, and informed consent. Further, selected trial data are monitored (e.g., inclusion, dropout, completion, primary outcome, trial medication, randomization, allocation, drug compliance, medicine accounting, AEs). No additional auditing is planned.

AEs and ARs related to the trial will be recorded in the CRF throughout the trial period, starting from the day of the first injection and ending at week 16. The relationship (causality) between the AE and the trial medication and severity will be assessed by the principal investigator or any one of the medical doctors trained in the protocol. The summary of product characteristics for Deca-Durabolin is used as a reference when assessing if a serious AR is unexpected or expected.

It should be noted that the following conditions are considered to occur often after hip fracture surgery and can lead to prolonged hospitalization: nausea, vomiting, dizziness, postoperative urine retention due to catheterization, pain or irritation in relation to the bladder due to catheterization, diarrhea, pneumonia and cardiopulmonary influence, hemoglobin (Hb) < 9.7 g/dl and consequently blood transfusion, and divergent blood tests due to surgery. These will not be registered as AEs during hospital admission. Expected pain from the operation site will not be registered as an AE during the trial period. Further, edema of the fractured limb is common in the postoperative period, and especially for patients with trochanteric fractures compared with those with cervical femoral fractures [4], and will not be reported as an AE. Laboratory test results beyond the reference interval will be recorded as an AE only if they cause a clinical action.

All AEs/ARs will be followed until stabilization by either the relevant hospital department or the patient's general practitioner.

Statistical analyses

Descriptive statistics will be used for presenting baseline characteristics. Continuous data will be examined for normality of distribution using Q-Q plots. Data will be presented as mean (SD) when normally distributed, otherwise as medians (q1–q3) or as frequencies with percentages.

The statistical analysis of the primary outcome will be two-sample t test or Wilcoxon rank-sum test as appropriate to determine systematical differences in change scores between the intervention and control groups. For the secondary outcomes, tests will be performed using either chi-square or Fisher's exact test for categorical data or two-sample t test or Wilcoxon rank-sum test for continuous data. Analysis of safety parameters and feasibility endpoints will be descriptive. The level of significance will be set at $P < 0.05$, and confidence intervals (CIs) will be displayed at 95% CI around differences.

The analysis will follow the intention-to-treat principle and include all randomized patients. To create a full analysis set, missing data will be imputed using a multiple imputation technique. Secondary analysis will be conducted for both primary and secondary outcomes on the per-protocol data, where patients are excluded if they are not compliant with the trial. Compliance in relation to per-protocol analysis is defined as 75% intake of nutritional supplement, 75% completed training sessions, and 100% received injections. No interim analyses will be conducted.

Ethics

The trial will be conducted in accordance with the principles of ICH-GCP and is monitored by the local GCP unit. The protocol is approved by the Capital Regions Research Ethics Committee (H-18004495) and the Danish Medicines Agency (EudraCT identifier 2017-001543-13). The trial is registered with the Danish Data Protection Agency (journal no. AHH-2017-090; I-Suite no. 05980).

All patients enrolled in the trial will have close contact with health professionals through weekly phone calls and hospital visits every 3 weeks. The increased attention, close contact, and strong focus on the individual patient's well-being can in itself be perceived as positive and thus beneficial. Risks and ARs for study participants are considered to be minimal. Strength training has been widely reported as safe [3, 13, 28, 58], and the planned program ensures a familiarization phase. Occurrence of ARs in relation to trial medication are not expected, owing to the relatively short intervention period and low doses. The safety precautions in the current trial, such as close observations through weekly interviews and assessment of safety parameters every 3 weeks, are considered to be sufficient to minimize risk and discomfort to the patient. However, slight soreness at the injection site could be experienced in relation to blood sampling and injection of trial medication. DEXA scans are conducted at two time points during the trial period. Radiation exposure is minimal, approximately 0.020 mSv corresponding to 1/50th of an X-ray of the lungs, and it constitutes no health risk.

On the basis of available evidence and the safety precautions taken in the present trial, the risk to the exposed patients seems to be absolutely minimal, and we are convinced that this trial is ethical to conduct. The participants do not receive remuneration for participation in the trial.

Protocol amendment

The following protocol amendments were approved by the ethics committee (28 September 2018) and the Danish Medicines Agency (26 October 2018):

1. The inclusion criterion *age* was changed from ≥ 65 years to ≥ 60 years. The cut ≥ 60 years is often used internationally when referring to elderly compared with nonelderly patients with hip fracture [59]. Further, patients from 60 to 64 years old would have the same potential benefit from the intervention.
2. The exclusion criterion concerning *PSA* values was changed, so assessment of PSA is moved to the 3-week control, because a falsely elevated PSA value could be seen during admission due to urine catheterization.
3. The exclusion criterion *terminal illness* was changed to *active cancer or suspected pathological fracture*.
4. The time frame for baseline testing was changed from 6–10 days to 3–10 days due to short hospitalization for some patients.
5. The intramuscular injection of trial medication was described to be administered in the gluteal muscle of the nonfractured leg. Due to difficulties with positioning all patients lying on the side, the description has been changed so that the medication can be administered either in the gluteal muscle or in the rectus femoris

A second protocol amendment concerning extension of the inclusion period until September 2020 has been approved by the ethics committee (27 September 2019) and the Danish Medicines Agency (22 July 2019). The primary investigator and the sponsor will inform the Research Ethics Committee, the Board of Health, and the Data Protection Agency if significant changes in protocol occur.

Dissemination

Two publications are planned for the HIP-SAP1 trial in peer-reviewed scientific journals. One is the protocol manuscript and the other is the primary trial report concerning feasibility and preliminary effects of the trial. Contributors to the trial will be offered authorship in accordance with the International Committee of Medical Journal Editors guidelines. There is no intention of using professional writers. Trial results will be published regardless of findings being positive, inconclusive, or negative. Further, results will be presented at national and international congresses. Trial participants will be notified of trial results by letter.

Discussion

Patients with hip fracture are a vulnerable group with high morbidity and mortality. They experience large strength deficits often leading to loss of function and independence. Knowledge regarding interventions enhancing outcome and reducing loss of function in this fragile group will be of immense benefit to both the individual patient in terms of better health and quality of life and the health care system in general.

The HIP-SAP1 trial is, to our knowledge, the first trial investigating the effect of a multimodal intervention consisting of physiotherapy (functional, balance, and strength training), protein-rich nutritional supplementation, and anabolic steroid in rehabilitation following hip fracture surgery. In the literature of rehabilitation following hip fracture, there is a demand for trials exploring the effect of multimodal interventions including muscle-enhancing medicine [6, 13, 21, 24, 25].

This study will contribute useful knowledge about the feasibility, safety, and preliminary effect of such multimodal intervention. If found feasible, this pilot trial will form the basis for a larger confirmatory trial that can finally determine the effect of muscle-building medicine in the rehabilitation of elderly patients with hip fracture, and it will contribute to setting new evidence-based standards for the optimal cross-continuum treatment following hip fracture. Potentially, this will bring a greater proportion of patients back to their previous level of functioning, which might lead to reductions in new falls and fractures, need of home care, and health care costs.

The design of this pilot trial being randomized and blinded, besides clarifying the question of feasibility, will give a preliminary suggestion of effect. Further, the preliminary estimates obtained for outcome parameters in this trial will be used for sample size calculation in a confirmatory trial. Continuing to undertake a larger confirmatory trial will not be based on a statistically significant difference between groups, because the trial is not sufficiently powered, but the results of the tests will be taken into consideration along with an overall assessment of all information provided by this pilot trial.

The intervention being initiated during admission and continued for 12 weeks in the municipality mimics everyday practice, and the physiotherapy intervention is very similar to the existing standard rehabilitation offered by the municipalities, which increases external

validity and will ease implementation. In regard to the nutritional component of the intervention, although an important focus area during hospitalization, it is not standard care in the municipalities to receive nutritional supplements for 12 weeks. However, the municipalities are aware of the importance of nutrition in this fragile group of patients. Some municipalities provide protein supplementation for all patients in relation to the exercise session; others conduct nutritional screening as part of the rehabilitation program, and patients in need of supplementation will be seen by a dietitian. On the basis of the current study design, we cannot make recommendations for the use of nutritional supplementation, but we will obtain information on adherence to the nutritional supplement. Knowledge obtained in this trial will inform a definitive trial.

The study is limited by narrow inclusion and exclusion criteria, and recruiting eligible patients might be difficult. The inclusion and exclusion criteria are based on previous studies using anabolic androgenic steroids in elderly patients [60, 61]. Because anabolic steroids are used in a novel field and the population is older and multimorbid, a rather conservative approach has been applied. Further, the criteria are decided on to get a comparable sample without too much "noise" from other factors that could influence outcome. If the trial is feasible and safe, less restrictive criteria might be applied for the larger confirmatory trial. The generalizability of the results of this trial will be limited to a similar population, and therefore the findings will apply only to a smaller proportion of patients with hip fracture.

Trial status

Protocol version 7 (19 December 2019). Screening for eligible patients began 5 June 2018, and the approximate date for completion of inclusion is September 2020.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3845-y.

Additional file 1. SPIRIT Checklist.

Additional file 2. Strength-training exercise logs used in the municipality.

Abbreviations

AE: Adverse event; AR: Adverse reaction; CRF: Case report form; DEXA: Dual x-ray absorptiometry; GCP: Good clinical practice; MNA-SF: Mini Nutritional Assessment–Short Form; NMS: New Mobility Score; PSA: Prostate-specific antigen; PT: Physiotherapy; REDCap: Research Electronic Data Capture; Reps: Repetitions; RM: Repetition maximum; VRS: Verbal Rating Scale

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Authors' contributions

SH drafted the protocol manuscript. HK, MTK, TB, and NBF drafted the original idea for this trial. All authors contributed to the trial design process. MTK is sponsor and has the main responsibility for completion of the trial. IB is the primary investigator and clinician. SH is project coordinator and responsible for the daily operation of the study (coordination between trial collaborators, screening and information of eligible participants, coordinating all trial related events, outcome assessor, data collection and management). IB, TAK, JEBJ, and NBF include patients and assess adverse events/reactions. All authors read and approved the final manuscript.

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Availability of data and materials

MTK owns data, and all authors will have full access to the dataset. A fully patient-anonymized dataset will be made available for the scientific journal reviewing the manuscript.

Ethics approval and consent to participate

Ethics approval was granted by the Capital Regions Research Ethics Committee (H-18004495) on 23 March 2018. Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
Sponsor, investigator, and others involved in the project are employed by Copenhagen University Hospital, Amager-Hvidovre, or Copenhagen University Hospital, Rigshospitalet, and they have no financial interest in the trial.

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Publisher's Note

Training schedule 1: Seated leg press (Week 1 – 6)

Name_____ Date start of training_____

Both legs are trained bilaterally

Date	Planned training	Pain at rest 0-4	Sets	Repetitions performed	Kilograms "lifted"	Pain during training 0-4	No/limited training
/	3 x 15 reps with 15RM		1.				
			2.				
			3.				
/	3 x 15 reps with 15RM		1.				
			2.				
			3.				
/	3 x 15 reps with 15RM		1.				
			2.				
			3.				
/	3 x 15 reps with 15RM		1.				
			2.				
			3.				
/	3 x 12 reps with 12RM		1.				
			2.				
			3.				
/	3 x 12 reps with 12RM		1.				
			2.				
			3.				
/	3 x 12 reps with 12RM		1.				
			2.				
			3.				
/	3 x 12 reps with 12RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				

Instructions:
Take as many repetitions (reps) as possible in each set.

If number of reps varies with more than 3 according to the planned, then adjust the load in the next set.

Both the concentric and eccentric phase is performed slowly and controlled.

Min. 1-minute rest between sets.

Verbal Rating Scale for pain: Fractured hip area:
0: No pain
1: Slight pain
2: Moderate pain
3: Severe pain
4: Unbearable pain

No/limited training:

Report reason if training / sets are not completed as planned:

1. Pain fractured hip area
2. Fatigue / exhaustion
3. Cancellation (report cause in scheme)
4. Training cancelled by center
5. Other (report cause in scheme)

Modified by Signe Hulsbæk, PT, PhD-student, 2018 after Morten Tange Kristensen, PT, Senior Researcher,
Departments of Physical Therapy and Orthopedic Surgery, Hvidovre Hospital, 2008.

Training schedule: Seated leg press (Week 7 – 12)

Name_____ Date start of training_____

Both legs are trained bilaterally

Date	Planned training	Pain at rest 0-4	Sets	Repetitions performed	Kilograms "lifted"	Pain during training 0-4	No/limited training
/	3 x 10 reps with 15RM		1.				
			2.				
			3.				
/	3 x 10 reps with 15RM		1.				
			2.				
			3.				
/	3 x 10 reps with 15RM		1.				
			2.				
			3.				
/	3 x 10 reps with 15RM		1.				
			2.				
			3.				
/	3 x 10 reps with 12RM		1.				
			2.				
			3.				
/	3 x 10 reps with 12RM		1.				
			2.				
			3.				
/	3 x 10 reps with 12RM		1.				
			2.				
			3.				
/	3 x 10 reps with 12RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				
/	3 x 10 reps with 10RM		1.				
			2.				
			3.				

Instructions:
Take as many repetitions (reps) as possible in each set.

If number of reps varies with more than 3 according to the planned, then adjust the load in the next set.

Both the concentric and eccentric phase is performed slowly and controlled.

Min. 1-minute rest between sets.

Verbal Rating Scale for pain: Fractured hip area:
0: No pain
1: Slight pain
2: Moderate pain
3: Severe pain
4: Unbearable pain

No/limited training:

Report reason if training / sets are not completed as planned:

1. Pain fractured hip area
2. Fatigue / exhaustion
3. Cancellation (report cause in scheme)
4. Training cancelled by center
5. Other (report cause in scheme)

Modified by Signe Hulsbæk, PT, PhD-student, 2018 after Morten Tange Kristensen, PT, Senior Researcher,
Departments of Physical Therapy and Orthopedic Surgery, Hvidovre Hospital, 2008.

Training schedule 1: Knee-extension (Week 1 – 6)

Name_____ Date start of training_____

Both legs are trained, unilaterally – non-fractured leg first

Date	Planned training	Pain at rest 0-4	Sets	Repetitions performed		Kilograms "lifted"		Pain during training 0-4	No/limited training
				Non-fractured	Fractured	Non-fractured	Fractured		
/	3 x 15 reps with 15RM		1.						
			2.						
			3.						
/	3 x 15 reps with 15RM		1.						
			2.						
			3.						
/	3 x 15 reps with 15RM		1.						
			2.						
			3.						
/	3 x 15 reps with 15RM		1.						
			2.						
			3.						
/	3 x 12 reps with 12RM		1.						
			2.						
			3.						
/	3 x 12 reps with 12RM		1.						
			2.						
			3.						
/	3 x 12 reps with 12RM		1.						
			2.						
			3.						
/	3 x 12 reps with 12RM		1.						
			2.						
			3.						
/	3 x 10 reps with 10RM		1.						
			2.						
			3.						
/	3 x 10 reps with 10RM		1.						
			2.						
			3.						
/	3 x 10 reps with 10RM		1.						
			2.						
			3.						
/	3 x 10 reps with 10RM		1.						
			2.						
			3.						

Instructions:
Take as many repetitions (reps) as possible in each set.

If number of reps varies with more than 3 according to the planned, then adjust the load in the next set.

Both the concentric and eccentric phase is performed slowly and controlled.

Min. 1-minute rest between sets.

Verbal Rating Scale for pain:
Fractured hip area:
0: No pain
1: Slight pain
2: Moderate pain
3: Severe pain
4: Unbearable pain

No/limited training:

Report reason if training / sets are not completed as planned:

1. Pain fractured hip area
2. Fatigue / exhaustion
3. Cancellation (report cause in scheme)
4. Training cancelled by center
5. Other (report cause in scheme)

Modified by Signe Hulsbæk, PT, PhD-student, 2018 after Morten Tange Kristensen, PT, Senior Researcher,
Departments of Physical Therapy and Orthopedic Surgery, Hvidovre Hospital, 2008.

Training schedule: Knee-extension (Week 7 – 12)

Name____ Date start of training____________________

Both legs are trained, unilaterally – non-fractured leg first

Date	Planned training	Pain at rest 0-4	Sets	Repetitions performed		Kilograms “lifted”		Pain during training 0-4	No/limited training
				Non-fractured	Fractured	Non-fractured	Fractured		
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						
/	3 x 10 repetitions with 10RM		1.						
			2.						
			3.						

Instructions:
Take as many repetitions (reps) as possible in each set.

If number of reps varies with more than 3 according to the planned, then adjust the load in the next set.

Both the concentric and eccentric phase is performed slowly and controlled.

Min. 1-minute rest between sets.

Verbal Rating Scale for pain: Fractured hip area:
0: No pain
1: Slight pain
2: Moderate pain
3: Severe pain
4: Unbearable pain

No/limited training:

Report reason if training / sets are not completed as planned:

1. Pain fractured hip area
2. Fatigue / exhaustion
3. Cancellation (report cause in scheme)
4. Training cancelled by center
5. Other (report cause in scheme)

Paper 3

Feasibility and preliminary effect of anabolic steroids in addition to strength training and nutritional supplement in rehabilitation of patients with hip fracture: a randomized controlled pilot trial (HIP-SAP1 trial).

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Feasibility and preliminary effect of anabolic steroids in addition to strength training and nutritional supplement in rehabilitation of patients with hip fracture: a randomized controlled pilot trial (HIP-SAP1 trial)

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Abstract

Background: Anabolic steroid has been suggested as a supplement during hip fracture rehabilitation and a Cochrane Review recommended further trials. The aim was to determine feasibility and preliminary effect of a 12-week intervention consisting of anabolic steroid in addition to physiotherapy and nutritional supplement on knee-extension strength and function after hip fracture surgery.

Methods: Patients were randomized (1:1) during acute care to: 1. Anabolic steroid (Nandrolone Decanoate) or 2. Placebo (Saline). Both groups received identical physiotherapy (with strength training) and a nutritional supplement. Primary outcome was change in maximal isometric knee-extension strength from the week after surgery to 14 weeks. Secondary outcomes were physical performance, patient reported outcomes and body composition.

Results: Seven hundred seventeen patients were screened, and 23 randomised (mean age 73.4 years, 78% women). Target sample size was 48. Main limitations for inclusion were "not home-dwelling" (18%) and "cognitive dysfunction" (16%). Among eligible patients, the main reason for declining participation was "Overwhelmed and stressed by situation" (37%). Adherence to interventions was: Anabolic steroid 87%, exercise 91% and nutrition 61%. Addition of anabolic steroid showed a non-significant between-group difference in knee-extension strength in the fractured leg of 0.11 (95%CI -0.25;0.48) Nm/kg in favor of the anabolic group. Correspondingly, a non-significant between-group difference of 0.16 (95%CI -0.05;0.36) Nm/Kg was seen for the non-fractured leg. No significant between-group differences were identified for the secondary outcomes. Eighteen adverse reactions were identified (anabolic = 10, control = 8).

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Conclusions: Early inclusion after hip fracture surgery to this trial seemed non-feasible, primarily due to slow recruitment. Although inconclusive, positive tendencies were seen for the addition of anabolic steroid.

Trial registration: Clinicaltrials.gov NCT03545347.

Keywords: Rehabilitation, Strength training, Nutritional supplement, Anabolic steroid, Hip fracture, Physical therapy, Physical function, Body composition

Introduction

Patients with a hip fracture are a vulnerable group with high morbidity and mortality. Sustaining a hip fracture leads to large strength deficits [1, 2], causing loss of function, disability and further falls [3–5]. As such, a hip fracture often result in loss of independence, change of residence, more fractures and high mortality rates [6–9], and constitutes a substantial economic burden to the health care system [10, 11]. Although positive effects on mobility of structured exercise interventions including strength training are reported [12–15], these interventions alone are insufficient to overcome the major long-term negative impact of a hip fracture on physical function [7]. Thus, it has been argued to investigate the effect of multimodal interventions including muscle-enhancing medicine [4, 9, 16, 17].

A Cochrane Review (2014) evaluated the effect of anabolic steroids in rehabilitation following hip fracture surgery on functional outcome and adverse events [18]. Positive tendencies were identified, but due to high risk of bias, further trials were suggested [18].

Consequently, and based on existing knowledge on rehabilitation following hip fracture [12, 13, 15] and review recommendations [4, 9, 12, 17, 18], we investigated an early multimodal intervention consisting of anabolic steroid, nutritional supplement and exercise, to enhance short and long term outcomes after a hip fracture.

Purpose

The aim of this pilot trial was to investigate the feasibility and preliminary effect of a 12-week intervention consisting of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement on knee-extension strength and function at 14-weeks follow-up after hip fracture surgery. Hypotheses are described in the protocol [19].

Methods

Trial design

This is the primary trial report for the HIP-SAP1 trial. A randomized (1:1), blinded, single-center, placebo-controlled, two-armed, parallel-group, superiority pilot trial. The trial was approved by the Capital Region's Research Ethics Committee (H-18004495) and the Danish Medicine Agency (EudraCT: 2017–001543-13) and registered with the Danish Data Protection Agency, Journal no.: AHH-2017-090, I-Suite No.: 05980. It adhered to the principles of ICH-GCP and was monitored by a local Good Clinical Practice (GCP) Unit. Reporting of the trial follows the CONSORT checklist [20], and the intervention is described according to the TIDieR checklist [21]. Pre-registration at ClinicalTrials.gov, registration number NCT03545347 (04/06/2018). The trial protocol was published December 23, 2019 [19].

Changes to method after trial commencement

The inclusion period was extended with 1 year due to slow recruitment. Nonetheless, the trial was prematurely discontinued due to slow recruitment. All other changes have been reported previously [19].

Participants

Patients admitted to the Hip Fracture Unit, at the Orthopedic Department, Hvidovre Hospital, University of Copenhagen was screened for eligibility from 5th June 2018 to 24th February 2020. Sampling method was consecutive, though screening was discontinued during trial staff's absence. A full list of eligibility criteria has been published previously [19]. Briefly, patients had to be aged 60 or above, prefracture home-dwelling, with indoor walking ability and without cognitive dysfunction (disoriented, dementia, delirium). Eligible patients were addressed at the ward 1–4 days post-surgery. Full oral and written information was provided by the project coordinator (PhD student and physiotherapist with 12 years' experience within hip fracture rehabilitation). Patients were offered at least 24 h to consider participation and had the opportunity of having a relative or other person accompanying for further information. Patients who agreed to participate signed an informed consent form.

Intervention

Patients were randomized (1:1) to one of two arms: 1. anabolic steroid (INT) or 2. placebo (CON). Both groups followed identical physiotherapy and nutritional supplement programs. A detailed intervention description has been published [19]. Below is a summery.

Trial medication

Active arm (INT) Every 3 weeks the patients received intramuscular injections of nandrolone decanoate (Deca-Durabolin 50 mg/ml produced by Aspen). First injection was administered at baseline and last injection at week 12. Women received 50 mg; men with total testosterone ≥11 nmol/l received 100 mg, and men with total testosterone < 11 nmol/l received a dose of 200 mg.

Placebo arm (CON) Following the same intervals as for the active agent, patients received a placebo injection of 1 ml Sodium Chloride 9 mg/ml (produced by Fresenius Kabi). The injection was administered at the same site as the active agent. The product has no medical therapeutic effect.

Nutritional supplement

Two daily nutritional drinks were offered during hospital admission as standard procedure. The protein-rich nutritional supplement was planned to account for at least 35% of the patient's daily protein requirement. The recommendations for geriatric patients with acute disease is 1.2–1.5 g/kg bodyweight/day [22]. The standard used at the hip fracture unit is 1.35 g/kg bodyweight/day. The protein-rich nutritional supplement is a liquid containing 18 g milk-based protein pr. bottle (Nestlé Resource 2.0 + fiber). Based on the standard used in this trial, patients received 2 bottles per day for 12 weeks.

Physiotherapy

Physiotherapy was started on postoperative day 1 and included functional exercises such as transfers and walking, as well as exercise therapy primarily aimed at lower extremities. An exercise guide of 12 exercises was handed out and progressed individually [1]. After discharge, patients were referred for physiotherapy in the municipality. The patients received physiotherapy 1 h twice a week, up to and including the 12th week after inclusion in the trial. The training session consisted of warm up, functional training, balance training, lower limb exercises and progressive strength training. Two strength training exercises were mandatory (knee-extension and leg press) and performed according to a standardized protocol with 3 sets of each exercise. In the first 2 weeks the number of repetitions was 15 with an intensity of 15 repetition maximum (RM), hereafter 2 weeks of 12 repetitions with 12 RM and for the remaining 8 weeks 10 repetitions with 10 RM [23]. The physiotherapist logged the load, number of repetitions and pain for each set during the session [19] and assisted the patient in progressing the load on a set to set basis if possible, or at least from session to session.

General trial treatment procedures

Patients included in the trial followed the departments standard procedures for surgery [24], anesthesia and peri-operative care. Standard perioperative care includes D-vitamin and calcium supplement dependent on the patient's individual level. After enrollment, baseline testing was carried out by the project coordinator. Due to the extensive test battery, baseline testing often extended over 2 days, within post-operative day 3–10. Patients were randomized after baseline testing. Hereafter, the first injection of the trial solutions was administered by a dedicated nurse. Throughout the trial, weekly telephone calls were conducted by the project coordinator to ensure and monitor compliance as well as detect potential adverse events. The patient visited the hospital every 3rd week, where blood tests was carried out, safety parameters assed and trial medication administered. The project coordinator and dedicated nurse undertook the assessments and medication administration. Further, nutritional supplement covering the following 3 weeks were handed out. Patients were offered free transportation.

Feasibility outcomes

The following feasibility aspects were assessed: Number of eligible patients, inclusion rate per month, feasibility and suitability of outcome measures, the acceptability to the patients of the treatments, adherence to the treatment, retention to the scheduled controls and follow-up, and number and severity of adverse events.

Outcomes of effectiveness

Blinded outcome assessment was conducted at baseline and at follow-up (week 14) by the project coordinator. Outcomes and time of assessment are described in detail in the published protocol [19]. Below is a short description.

Primary outcome

Change in maximal isometric knee-extension strength (Nm/Kg) in the fractured limb from baseline to 14-week follow-up was measured using a belt fixated handheld dynamometer (Commander Muscle Tester; JTech Medical Utah, USA) [1, 23, 25]. The test is conducted as described in the protocol with the patient seated on the bedside, hips, and knee joint angle in 90° flexion and hands placed on the mattress for support [19].

Secondary outcomes

Performance measures, patient reported outcomes (PROM's), measures of body composition, hormone levels and lipid profile are described in eMethods in Additional file 1 and published previously [19].

Safety parameters

Safety parameters were assessed at baseline, 3,6,9,12,14 weeks after inclusion.

The following blood tests were assessed: Hemoglobin, hematocrit, creatinine, carbamide, sodium (Na+), potassium (K+), calcium, INR (P-Coagulation), liver tests, PSA, glucose. Safety thresholds were defined for the following 3 parameters: Hematocrit (safety threshold: Values > 0.50); liver tests (safety threshold: If liver test values are > 3 times the upper limit of normal); PSA (safety threshold: If PSA increases to more than 50%). Other safety parameters were: Blood pressure, facial hirsutism (Ferriman-Galwey hirsutism score,2 face related items) [26], hoarseness, edema in non-fractured leg, falls. If values exceeded the safety thresholds the treatment with Deca-Durabolin was discontinued. Further, if women experienced displeasing androgenic side effects, treatment was discontinued.

Adverse events (AE) and reactions (AR) including severity and expectedness was recorded throughout the trial period in accordance with European guidelines [27] as described in the protocol [19].

Sample size

Sample size calculation for the primary outcome; change in knee-extension strength of the fractured limb, were made to detect a between-group difference in the change score of 0.2 Nm/kg in favor of the intervention group using Lehr's formula with an SD of 0.22 Nm/kg [1, 19]. Based on these estimates, 20 patients were needed in each group using a standard of 80% power and type 1 error rate of 5%. To allow for a 20% dropout rate, 48 patients were planned for inclusion.

Randomization and allocation

The patients were randomly assigned using a 1:1 allocation ratio. Block randomization (blocks of 2 and 4) was performed and patients were stratified for type of fracture and sex. The allocation sequence was computer generated (random number generator) by a qualified person not involved in the trial. The allocation sequence was retained in a locked cabinet by the person generating the sequence. To ensure allocation sequence concealment, sequentially numbered, opaque, sealed envelopes were used. When a patient entered the trial, the coded envelope was broken by the nurse injecting the trial medication and the envelope was retained by the nurse.

Blinding procedure

The patients, the healthcare providers, intervention deliverers, data collectors, outcome assessors were all blinded to group allocation. The only person not blinded were the dedicated nurse drawing the envelope and injecting the trial medication.

Statistical analyses

Descriptive statistics are used to present baseline characteristics. Primary and secondary outcomes are presented as mean (SD) for the sake of simplicity, although normality of distribution is difficult to assess when dealing with small samples. Mean within-group and between-group differences are reported with 95% confidence intervals (CI) and analyzed using a 'Two sample t-test' or 'Wilcoxon rank sum' depended on our best judgement of normality of distribution of the change score. The primary analysis involved all randomly assigned patients with data ("available cases", $n = 21$) and is here referred to as modified intention-to-treat analysis. Due to the small sample size, missing data was not imputed. The level of significance was set at $p < 0.05$.

Secondary per-protocol analyzes were conducted for the primary outcome, excluding patients with less than 75% adherence to training sessions and 80% received injections (in the protocol 100% adherence to injections was stated, which seems unrealistic high, and has been corrected). Since intake of the nutritional supplement was low, no per-protocol analysis was conducted based on the nutritional intake.

Results

Recruitment and feasibility

Out of 717 screened patients, 29 were included from 6th of June 2018 until 24th February 2020 equivalent to 89 weeks (Fig. 1). Inclusion was discontinued for 23 weeks due to trial staff absence, resulting in an actual inclusion period 16.5 months, equivalent to an inclusion rate of approximately 1.8 patients per month. Reasons for non-participation are presented in eTable 1 (Additional file 1), and the two most dominant reasons were "not home-dwelling" (18%) and "cognitive dysfunction" (16%). The number of patients declining to participate in the trial was 41, and the most common reason was "Overwhelmed and stressed by situation (37%) (eTable 2, Additional file 1). Thus, only 23 patients could be randomized; 12 patients were allocated to INT and 11 to CON (Fig. 1). One patient in each group dropped out within the first 2 weeks and both declined participation in the follow-up assessment.

Baseline data

Mean age of the randomized participants was 73.4 (6.7, range 62–85) years and 78% were women. In comparison, the mean age of 717 screened patients were 78.3 (12.2) with 66% women. Participants in general had a high prefracture functional level and 91% were discharged home after median 8 (7–9) days hospitalization. No important differences were identified between INT and CON at baseline (Table 1).

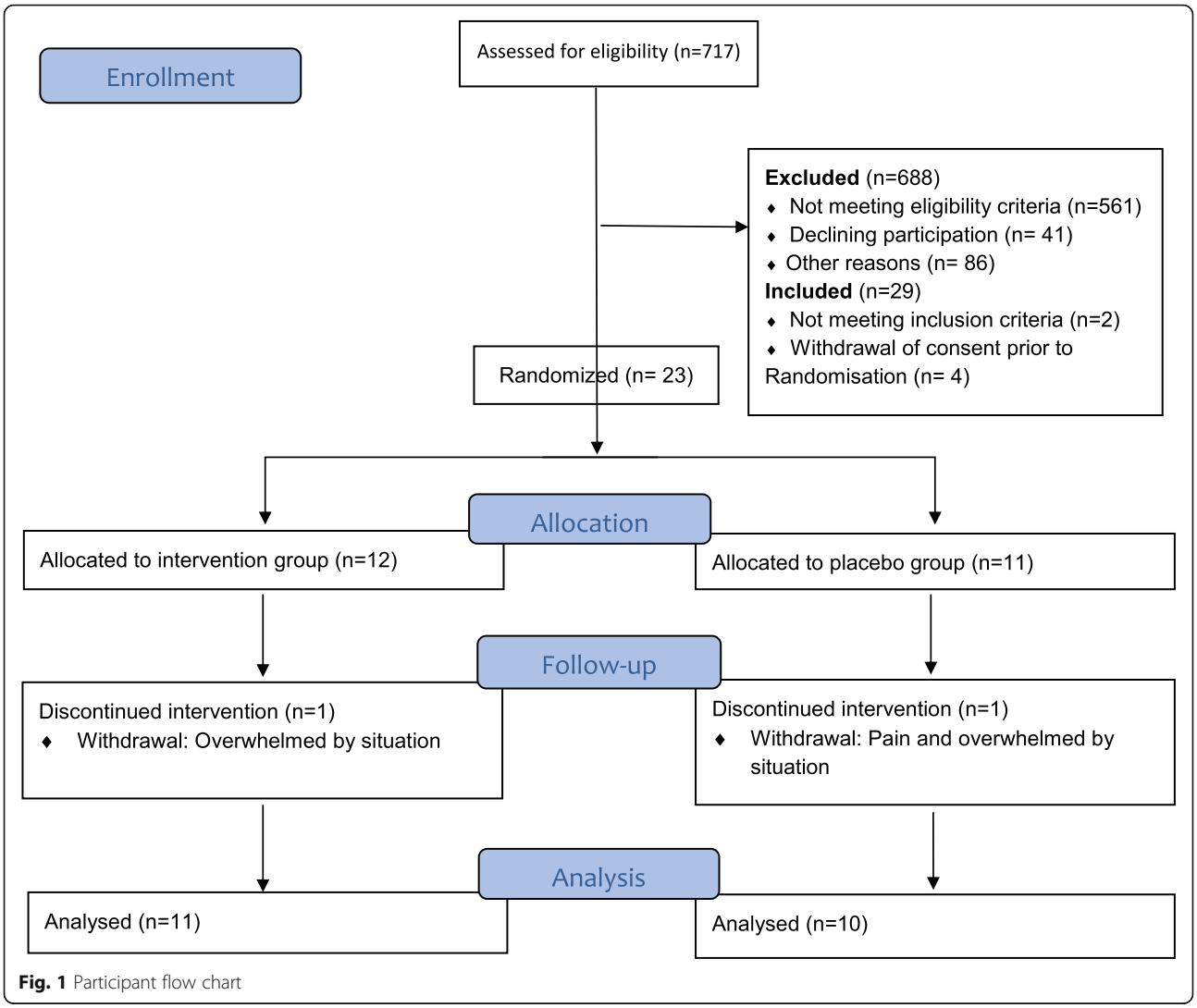

Fig. 1 Participant flow chart

Adherence

Medication

Six out of the 21 participants did not receive all 5 injections of the trial solutions; 5 where in the INT and 1 in the CON. Of the 5 in the INT, 1 stopped after 2 injections due to covid-19 and the risk of getting infected by contact to hospital staff, 1 stopped after 2 injections due to a non-related event (myocardial infarction – pre-existing coronary stenosis), 1 stopped after 2 injections because of increased liver parameters (classified as related), 1 stopped after 3 injections due to increased perspiration and facial hirsutism (related) and 1 missed 1 injection due to slightly increased PSA value (related). Further, 1 in the CON stopped after 3 injections due to increased liver parameters. Summed up, adherence to injections was 87%.

Exercise

The 21 patients exercised in 9 different rehabilitation centers in the uptake area of the hospital. Due to Covid-19 lockdown, 3 patients discontinued the planned exercise intervention in the municipality. These patients were instructed in home exercises (sit to stand, steps/stairs, hip exercises for abductors and extensors) and encouraged to stay as active as possible given the extraordinary situation. However, walking outside their home was restricted to a minimum. Generally, adherence to the municipality-based physiotherapy was excellent with 91%, and with an average of 21.3 (2.3) exercise sessions offered by the municipalities for the remaining 18 participants. Correspondingly, attendance to exercise sessions were 19.4 (2.1), while 1.8 (1.2) sessions were canceled by participants. Adherence to the progressive strength exercises were good, although 5 participants paused their knee-extension exercises due to pain for 1 to 4 sessions. Two of these participants also paused leg press simultaneously. During the first strength training session load-values varied a lot, since the therapist had to find the right load-level, therefore the load progression for

Table 1 Baseline characteristics of randomized participants ($n = 23$)

	Intervention ($n = 12$)	Control ($n = 11$)
Women n (%)	9 (75)	9 (82)
Men n (%)	3 (25)	2 (18)
Age (years), mean (SD)	73.5 (5.9)	73.4 (7.7)
Body weight (kg), mean (SD)	74.5 (12.4)	77.4 (18.5)
American Society of Anesthesiologist Grade (ASA), mean (SD)	2.1 (0.67)	1.9 (0.30)
Number of pre-existing diagnoses [a], mean (SD)	2.9 (2.5)	2.6 (1.1)
Fracture type, n (%)		
Intracapsular	9 (75)	7 (64)
Extracapsular	3 (25)	4 (36)
Type of surgery, n (%)		
2 pins	0	1 (9)
Hemi/total arthroplasty	8 (67)	6 (55)
Dynamic hip screw	1 (8)	1 (9)
Intra medullar hip screw	3 (25)	3 (27)
Living alone, n (%)	7 (58)	6 (55)
Prefracture homecare	1 (8.3)	1 (9.1)
New Mobility Score, 0–9 points (prefracture), mean (SD)	8.6 (0.8)	8.5 (1.0)
Walking aid indoor, (prefracture), n (%)	0	1 (9)
Walking aid outdoor, (prefracture), n (%)	2 (17)	2 (18)
Discharged home, n (%)	11 (92)	10 (91)
Length of stay (days), median (q1-q3)	8 (6–9)	8 (7–9)

[a]Retrieved from hospital chart

the first 2 weeks (15RM-period) is calculated from the 2nd to the 4th session. Training loads progressed satisfactorily within the different RM levels, as shown in eTable 3, additional file 1.

Nutritional supplement

Average consumption of nutritional supplement was 61% of the planned 168 drinks, and with no significant difference between-groups (INT 58.5% vs CON 63.4%). Two participants did not want to drink the supplement at all. Nine out of 21 participants consumed more than 75%. The most frequent reason for non-consumption was loss of appetite, nausea, dislike taste and reflux.

Hospital controls

Only 1 participant did not attend 3 of the scheduled controls due to Covid-19 lock-down (participants own decision), but attended the final follow-up. However, some patients expressed that getting out of the house and back and forth to the hospital was strenuous, during the first hospital visits. On the contrary, many patients expressed gratitude and felt good taken care of, due to the extra controls.

Feasibility and suitability of outcome measures

The extensive number of measurements was time-consuming and exhausting to many of the participants at baseline and therefore testing often took place over 2 days. Still, high completeness of data suggest that it was feasible. The New Mobility Score (NMS), The Short Falls Efficacy Scale–International (FES-I), Geriatric Depression Scale (GDS) and Mini Nutritional Assessment–Short Form (MNA-SF) showed some ceiling effect. Some of the PROM's were a bit overlapping, and in future studies GDS could be left out as depression and anxiety to some extend are included in EQ-5D. DEXA-scanning during the first week after surgery was challenging for participants, as mobility was limited and they were restricted by pain.

Primary outcome

Knee-extension strength of the fractured and non-fractured leg improved significantly in both groups from baseline to 14-week follow-up. Between-group difference of the fractured leg was insignificant 0.11 (95%Cl − 0.25; 0.48) Nm/kg in favor of the INT (Table 2). The median percentage change in knee-extension strength of fractured leg was 178% (41–263) for INT and 50% (20–173) for CON ($p = 0.28$). Corresponding, between-group

Table 2 Analysis of primary outcome, knee-extension strength ($n = 21$)

Primary outcome	Baseline Mean (SD)		Follow-up Mean (SD)		Within-group difference Mean (95% CI)		Between-group difference Mean (95% CI)
Modified intention-to-treat							
	INT ($n = 11$)	**CON ($n = 10$)**	**INT ($n = 11$)**	**CON ($n = 10$)**	**INT ($n = 11$)**	**CON ($n = 10$)**	
Strength, Fractured (Nm/kg)	0.56 (0.38)	0.72 (0.36)	1.17 (0.46)	1.23 (0.39)	0.61 (0.34;0.88)	0.50 (0.21;0.79)	0.11 (− 0.25; 0.48)
Strength, non-fractured (Nm/kg)	1.07 (0.45)	1.27 (0.26)	1.35 (0.39)	1.40 (0.39)	0.28 (0.20;0.37)	0.13 (− 0.07;0.32)	0.16 (− 0.05; 0.36)
Strength, fractured % non-fractured (%)	50.5 (21.6)	59.4 (31.0)	84.6 (15.4)	89.1 (16.2)	34.1 (16.5;51.6)	29.7 (9.0;50.3)	4.4 (−20.7; 29.5)
Per protocol							
Exercise[a]	**($n = 8$)**	**($n = 10$)**	**($n = 8$)**	**($n = 10$)**	**($n = 8$)**	**($n = 10$)**	
Strength, Fractured (Nm/kg)	0.62 (0.42)	0.73 (0.37)	1.35 (0.40)	1.23 (0.39)	0.72 (0.42;1.03)	0.50 (0.21;0.79)	0.23 (−0.16; 0.61)
Strength, non-fractured (Nm/kg)	1.15 (0.50)	1.27 (0.26)	1.45 (0.40)	1.40 (0.39)	0.29 (0.19;0.40)	0.13 (− 0.07;0.32)	0.17 (− 0.04; 0.37)
Injections	**($n = 7$)**	**($n = 9$)**	**($n = 7$)**	**($n = 9$)**	**($n = 7$)**	**($n = 9$)**	
Strength, Fractured (Nm/kg)	0.36 (0.17)	0.69 (0.37)	1.14 (0.45)	1.25 (0.40)	0.78 (0.47;1.09)	0.56 (0.26;0.85)	0.22 (−0.17;0.61)
Strength, non-fractured (Nm/kg)	1.00 (0.48)	1.29 (0.26)	1.33 (0.39)	1.39 (0.41)	0.33 (0.23;0.42)	0.10 (−0.11;0.31)	0.22 (0.01;0.44)*
Exercise + injections	**($n = 5$)**	**($n = 9$)**	**($n = 5$)**	**($n = 9$)**	**($n = 5$)**	**($n = 9$)**	
Strength, Fractured (Nm/kg)	0.38 (0.17)	0.69 (0.37)	1.27 (0.48)	1.25 (0.40)	0.89 (0.49;1.29)	0.56 (0.26;0.85)	0.34 (−0.10;0.77)
Strength, non-fractured (Nm/kg)	1.05 (0.57)	1.29 (0.26)	1.36 (0.47)	1.39 (0.41)	0.32 (0.18;0.46)	0.10 (−0.11;0.31)	0.22 (−0.07;0.50)

Cases removed if adherence below 75% for exercise (pre-defined) and 80% for injections (pre-defined as 100% but changed to 80% as this was reached by only one missing injection)

INT intervention (anabolic group), *CON* control group

[a] 3 participants non adherent to exercise due to Covid-19 lock-down

* $P = 0.046$ (Sattertwaite due to unequal variance)

difference of the non-fractured leg was insignificant 0.16 (95% CI -0.05;0.36) Nm/Kg, with a median percentage change in knee-extension strength of non-fractured leg of 31% (12–53%) for INT and 8% (0–33) for CON ($p = 0.04$). Per protocol analysis of participant's adherent to exercise ($n = 18$), injections ($n = 16$) and to both exercise and injections ($n = 14$) are presented in Table 2. Between-group differences in knee-extension strength increased in all 3 analysis for both fractured and non-fractured leg.

Secondary outcomes

No significant between-group differences were identified for any of the secondary performance measures or patient reported outcomes (eTable 4, additional file 1). Increase in plasma testosterone for the INT was median 3.9 (1.2;7.5) nmol/l and for the CON 0.15 (0;0.4) nmol/l, median between-group difference was 3.7 nmol/l ($p = 0.04$, Wilcoxon rank sum test). Otherwise, no significant differences were identified for any of the other hormone parameters, cholesterol, CRP or body composition (eTable 4, additional file 1). Physical activity monitored after ceased intervention showed an in-significant between-group difference 0.68 (− 1.42; 2.79) hours/day in upright time (eTable 5, additional file 1).

Adverse events

Fifty-seven adverse events were registered, 27 in INT and 30 in CON. Fifty-four events were categorized as non-serious and 3 as serious (1: Myocardial infarction (preexisting coronary stenosis, treated with stent), 2: 24-h hospital stay because of hip fracture-related pain, 3: Extended hospitalization due to infection). Of the 57 events 39 were categorized as non-related (eTable 6, additional file 1) and 18 as related (Adverse reactions, Table 3), the summary of product characteristics for Deca-Durabolin was used as reference.

Discussion

The HIP-SAP pilot trial is to our knowledge the first trial investigating the feasibility and preliminary effect of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement in rehabilitation following hip fracture surgery. The trial provides important knowledge on feasibility, that will help inform future trials emphasizing the difficulties to perform interventional studies in this frail patient population. Acute hospital recruitment was difficult and seem to be a major limitation in the current trial design. On the contrary, adherence to injections and exercise was high, 87 and 91% respectively, indicating excellent acceptability of the

Table 3 Adverse reactions by group[a]

Event	INT	CON
Increased lever parameters	1	2
Increased cholesterol parameters (+triglyceride)	3	2
Increased sweating	1	1
Nausea	1	1
Edema + (foot ulcer, upper side from edema)	1	
Rasch		1
Increased PSA	1	
Hirsutism	1	
Increased blood pressure	1	
Increased libido		1
Total	10	8

[a]Categorized as potentially related to anabolic steroid prior to un-blinding

intervention. Although inconclusive due to the small sample size, promising tendencies were seen for the addition of anabolic steroid on primary outcome of knee-extension muscle strength.

Recruitment

The inclusion rate of approximately 1.8 patients pr. month was low and less than half of what we expected based on a previous RCT [1], but comparable to trials with similar interventions [28–30]. The two most dominant reasons for non-eligibility were "not home-dwelling" (18%) and "cognitive dysfunction" (16%). Of eligible patients 41% was included. The most frequent reason to decline participation was feeling 'Overwhelmed and stressed by situation'. It is well known that recruitment efficacy declines with increasing age of the population, and often inclusion targets are not met in populations of acute hospitalized geriatric patients [31–33]. For hip fracture patients the first postoperative days are characterized by fatigue, pain, dullness from medication. They experience a severe decline in mobility, increased dependency and many are concerned with life after the fracture [34, 35]. The highly accelerated acute hospital stay (median 8 days), left few post-operative days and little time for inclusion and outcome assessment, in addition to the many standard clinical procedures during admission. Therefore, being in a stressful situation with little time to consider participation might have impeded recruitment, and some patients asked for the possibility to consider participation and decide when back home. Positively and contrary to our anticipations, worries about adverse events related to trial medication, was not a major issue for this population.

In this trial, rather conservative eligibility criteria were applied, since the use of anabolic steroid is novel in this multimorbid patient group. Less restrictive eligibility criteria could be considered in future trials, e.g. patients residing at nursing homes or those with mild cognitive dysfunctions, might be able to participate, when situated in known surroundings, and with the right support [36]. Postponing inclusion and 'Consent by proxy' should be considered to increase inclusion rate. Acute illness as a result of surgery e.g. renal impairment may also be modified by later inclusion.

Adherence

Adherence to injections and physiotherapy with strength training was excellent and interpreted as an expression of good acceptability of the interventions. During the physiotherapy intervention, patients were able to progressively increase loads in the strength exercises throughout the trial period, supporting acceptability of intervention. On the contrary, adherence to the nutritional supplement was lower than expected (61%), but comparable to similar trials [37, 38]. The patients described loss of appetite, nausea and disliking taste as the most frequent barriers for consumption. Loss of appetite and nausea could be a consequence of surgical stress and opioid treatment and not necessarily related to the product. Malnutrition is a modifiable potential risk factor for poor outcomes following hip fracture surgery [22, 37]. Serum albumin concentration is the most commonly used serum marker of malnutrition, in which patients are considered to be malnourished when serum albumin concentrations are < 35 g/L [39]. Given the albumin levels at baseline (mean of 25.9 g/L (2.8)) all patients were malnourished (eTable 7, additional file 1). At follow-up albumin values had increased to 39.3 g/L (3.3). None of the patients were malnourished when assessed by MNA-SF at baseline and only 5 patients were at risk of malnutrition. A consideration for future trials, is to individualize type of supplement and provided it only for patients at nutritional risk.

The retention to hospital controls was excellent, although some patients experienced getting out of the house and the transportation as strenuous. Home visits could be considered in future trials, or maybe a different form of anabolic steroid preparation, of which the patients or home care could administer.

Preliminary effect of primary and secondary outcomes

Although inconclusive, some tendencies were seen for the addition of anabolic steroid on the primary outcome of knee-extension muscle strength and in favor of INT in the modified intention-to-treat analysis. Also, in per protocol analyses, between-group differences for participant's adherent to the anabolic steroid almost reached significance for the non-fractured leg ($p = 0.046$) in favor of INT.

Overall, a tendency of larger strength improvements was seen in the non-fractured leg compared to the fractured leg, probably due to less variance caused by trauma and surgery related pain and edema [2, 40].

However, pain was not a limiting factor during strength-testing. At baseline only 2 in INT and 4 in CON expressed moderate to severe pain (VRS > 1), at follow-up no patients reported moderate to severe pain (eTable 8, additional file 1).

Disappointingly, no significant between-group difference was identified for secondary performance- or patient reported measures, while significant positive within-group changes were seen for gait, mobility and fear of falling, as expected. No within-group change were seen for hand grip strength, QoL, fatigue, depression, as in line with similar previous studies [23, 41, 42]. Testosterone levels for both genders were very low at baseline, but as expected higher levels of testosterone were found in the INT at follow-up.

Several studies report decline in BMD following hip fracture [43–45]. Positively, INT showed a significant increase in whole body BMD of 0.019 g/cm^2 whereas it decreased for CON (– 0.015 g/cm^2). A previous study also showed positive effect of 6 months treatment with nandrolone on LBM in elderly female hip fracture patients [46], but no significant between-group differences were seen for measures of LBM in the present study. The lack of effect is probably explained by short treatment period as well as low sample size. Weight loss in both groups can to some extent be explained by post-surgery edema and fluid retention at baseline, which is in line with the reduction in total LBM and in accordance with previous studies showing a reduction in LBM of 3.4–6.4% from 3 days after surgery until 2 months [43, 44].

Adverse events

Adverse events and adverse reactions were equally distributed in the two groups. Female hirsutism following anabolic treatment have been reported in a previous study [30] and was a concern. Only one woman reported a slight increase in facial hair growth on the chin, but she used to shave prior to trial, and was not concerned with it, nonetheless injections were stopped as she was bothered with increased perspiration. Three patients had increased liver parameters, 2 (one in each group) with levels above the safety threshold, and medication was ceased. In both cases parameters were normalized within 2 weeks.

Strength and limits

A methodological strength is the trial design being a randomized blinded placebo-controlled trial. Further the deliverance of the exercise intervention mimics everyday practice, with initiation of the intervention during admission in the acute setting and continuing in the municipality for approximately 12 weeks. The content of the physiotherapy intervention is similar to the existing standard rehabilitation offered by the municipalities, which increases external validity and could ease implementation. Further, we consider it at a major strength, that progressive strength training were demonstrated to be feasible and with high adherence, since strength training is crucial for patients with hip fracture as loss of muscle strength is a serious consequence of the fracture, but also since pre-existing sarcopenia is prevalent in this population [47].

The trial is limited by the low inclusion rate, as we were not able to reach the calculated number needed in the trial. Thus, we were not able to conclude for or against the intervention. Further, the participants included were younger and had a higher prefracture functional level compared to the general population of older hip fracture patients admitted from own home [48]. Consequently, generalizability of the results will be limited to a similar population. However, even the fitter hip fracture patients have strength deficits and potential for improving strength and function. In a recently published study, we found that almost half of hip fracture patients were classified as probable sarcopenic using cut-points for knee extension strength of the non-fractured leg and hand grip strength [49]. Furthermore, a study by Dyer et al. [7] showed that among the fitter patients, only 40–44% recovered their pre-fracture mobility independence.

Another limitation is not involving participants in the design of the study, which was not possible due to limited resources and the complexity of the trial.

Conclusion

Early inclusion after hip fracture surgery to this cross-continuum drug trial investigating the effect of anabolic steroid during rehabilitation seemed non-feasible, primarily due to a low inclusion rate. The trial illustrates the complexity of challenges related to carrying out randomized controlled trials in patients with hip fracture. Although inconclusive due to the small sample size, promising tendencies were seen for the addition of anabolic steroid.

Abbreviations

INT: Intervention group; CON: Control group; RM: Repetition maximum; ICH-GCP: International conference on harmonisation - good clinical practice; VRS: Verbal rating scale; NMS: New mobility score; NYHA: New York Heart Association; PSA: Prostate specific antigen; HGS: Hand-grip strength; DEXA: Dual x-ray absorptiometry; BDM: Bone mineral density; LBM: Lean body mass; MNA-SF: Mini nutritional assessment short form; TUG: Timed up and go; DEMMI: The de mortons mobility index; HRQoL: Health related quality of life; Short FES-I: Short falls efficacy scale – international; GDS-15: Geriatric depression scale; CRF: Case report form; REDCap: Research electronic data capture; GCP: Good clinical practice; SOP: Standard operating procedure; AE: Adverse event; AR: Adverse reaction

Supplementary Information

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Additional file 1. Supplementary material (eMethod and eTables 1–8).

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Authors' contributions
SH drafted the manuscript and all authors have revised and approved the manuscript. HK, MTK, TB and NBF drafted the original idea for this trial. All authors contributed in the trial design process. MTK was sponsor and the main responsible for completion of the trial. IB was primary investigator. SH was project coordinator and responsible for the daily operation (coordination between trial collaborators, screening and information of eligible participants, coordinating all trial related events, outcome assessor, data collection and management). IB, JEBJ and NBF included participants, and assesses adverse events/reactions.

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Availability of data and materials
MTK owns data, all authors have full access to the dataset. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval has been granted by the Capital Regions Research Ethics Committee (H-18004495) on the 23rd of marts 2018. Informed consent was obtained from all study participants.

Consent for publication
Not applicable.

Competing interests
TB declares to have received speaker's honoraria for talks or expert testimony on the efficacy of exercise therapy to enhance recovery after surgery at meetings or symposia held by biomedical companies (Zimmer Biomet and Novartis). All other authors declare that they have no competing interests. Sponsor, investigator, and others involved in the project are employed by Copenhagen University Hospital, Hvidovre, or Copenhagen University Hospital, Rigshospitalet, and they have no financial interest in the trial.

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Publisher's Note

Supplementary material

Feasibility and preliminary effect of strength training, nutritional supplement and anabolic steroids in rehabilitation of patients with hip fracture: A randomized controlled pilot trial (HIP-SAP1 trial)

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Content:

eMethods:

Description of secondary outcome measures

Unless stated otherwise, the change in values are measured from baseline until 14 weeks.

Performance measures

Maximal isometric knee-extension strength (Nm/Kg) in the non-fractured limb. Maximal isometric knee-extension strength (Nm/Kg) in the fractured limb in % of the non-fractured limb. Hand-grip strength (HGS) measured in Kg. in the dominant hand, using a digital handheld dynamometer (Saehan Grip, DHD-1). Gait speed in m/s was assessed using the 10-meter fast speed walking test, standing start (10mWT) [1]. Timed up and go test (TUG) measured in seconds (and 10mWT) was performed preferable using a 4-wheeled rollator if not possible the walking aid the patient was able to manage independently [2,3]. The de Mortons Mobility Index (DEMMI), score range from 0 to 100, 100 representing the highest level of mobility [4–6]. Physical activity as sedentary time (lying/sitting) and upright time (standing/walking),

steps and transfers is measured using a body-worn accelerometer activity monitor (ActivePAL) [7]. The patient wore the monitor for one week following the 12-week control.

Patient reported outcomes
Nutrition screening using the Mini Nutritional Assessment Short Form (MNA-SF), range 0-14, high scores indicating better nutritional status [8,9]. Functional level was assessed by the modified New Mobility Score (NMS), range 0-9, higher score indicating higher independence (baseline assessment refers to prefracture status) [10–12]. EQ-5D-3L assessing Health Related Quality of Life (HRQoL), baseline assessment refers to the time prior to the fracture [13–15]. Hip fracture related pain at rest and during outcome assessment is evaluated by Verbal Rating Scale (VRS), 0-4 [16]. The Short Falls Efficacy Scale-International (Short FES-I) measured fear of falling (score range from 7–28, higher scores indicating a higher fear of falling) [17,18]. Fatigue was assessed using the SF36 vitality subscale, consisting of 4 items, score range from 0-100, high score defines a more favorable health state, baseline assessment refers to pre-fracture state [19,20]. Depression is assessed using the Geriatric Depression Scale (GDS-15), administered as an interview, score range 0-15, baseline assessment refers to pre-fracture status [21,22].

Dual x-ray absorptiometry (DEXA)
Bone mineral density (BMD) of total body, total hip, femoral neck and lumbar spine. BMD is expressed in g/cm^2 and T-score was registered. Lean body mass (LBM) of total body, legs bilaterally and arms bilaterally expressed in kg. Total body fat mass expressed in kg.

Blood tests
Total testosterone (nmol/l), Luteinizing hormone, LH (IU/l), Follicle-stimulating hormone, FSH (IU/l), Sex hormone binding globulin, SHBG (nmol/l). Lipid profile (Total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride), mmol/l. C-reactive protein (CRP), mg/l.

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eTable 1: Numbers and reasons for non-participation (n=688)		
Reason		**Numbers (%)**
1	Age <60 years	64 (8.9)
2	Not Speaking and understanding Danish or having a Danish Social Security Number.	21 (2.9)
3	Unable to give informed consent (see point 11)	-
4	Residing at nursing home/24-hour rehabilitation prefracture.	130 (18.1)
5	No Independent pre-fracture indoor walking ability (NMS<2)	6 (0.8)
6	Weight-bearing restrictions	22 (3.1)
7	Multiple fractures	26 (3.6)
8	Active cancer or suspected pathological fracture	33 (4.6)
9	Patients unable/unwilling to cooperate for testing and rehabilitation	38 (5.3)
10	Planned/elective hospitalization within the trial period.	4 (0.6)
11	Cognitive dysfunction (disoriented, dementia, active delirium)	117 (16.3)
12	Uncontrolled blood pressure (systolic > 150 mmHg, or diastolic > 100 mmHg)	5 (0.7)
13	Heart disease (peri-, myo- or endocarditis)	0
14	History of stroke with motor disability.	22 (3.1)
15	Heart failure (NYHA class III and IV)	3 (0.4)
16	Kidney failure or renal impairment	40 (5.6)
17	Abnormal liver function tests or history of hepatic tumor	3 (0.4)
18	Elevated hematocrit ≥ 50%	0
19	History of breast or prostate cancer	25 (3.5)
20	Abnormally elevated serum PSA assessed at the 3-week control	1 (0.1)
21	Allergic to ingredients in the Deca-Durabolin solution or the nutritional supplement.	1 (0.1)
22	Transferred to another department	3 (0.4)
23	Living outside uptake area	66 (9.2)
24	Not drinking p-drink (prior to loosing this criteria)	1 (0.1)
25	Declining participation	41 (5.7)
26	Estrogen tablet treatment	1 (0.1)
27	Acute postoperative illness (nonspecific to other criteria's)	9 (1.3)
28	Admitted after surgery in another hospital	2 (0.3)
29	Fast discharge	3 (0.4)
30	Died in hospital	1 (0.1)
Note. NMS: New Mobility Score, NYHA: New York Heart Association; PSA: Prostate-specific antigen		

eTable 2: Patient-reported reasons for declining participation although fulfilling inclusion criteria (n=41)		
Reasons	**Primary**	**Secondary**
Overwhelmed and stressed by situation	15	1
Extra hospital controls	6	3
Disliking principle of randomization	1	4
Personal factors (e.g. a sick relative, job)	6	-
Worries related to adverse events	2	2
Disliking protein	-	2
Generally abstaining from medication	3	1
Relatives did not want patient to participate	3	-
No eyeglasses – couldn't read information and consent.	1	-
Did not want rehabilitation	-	1
Did not want information	4	-
Total	**41**	**14**

eTable 3: Progression in training loads in percentage [a]			
	n	**Median (q1; q3) % Increase**	**Range % Increase**
Session 2 – 4, 15 repetition maximum			
Knee extension, fractured	18	31.5 (10; 67)	0; 250
Knee extension, non-fractured	9 [b]	14 (0; 18)	0; 63
Leg press, bilateral	18	20 (9; 58)	-17; 133
Session 5 – 8, 12 repetition maximum			
Knee extension, fractured	18	18 (0; 59)	-41; 80
Knee extension, non-fractured	9	17 (9; 33)	6; 65
Leg press, bilateral	18	7.5 (0; 17)	0; 100
Session 9 – 10 repetition maximum			
Knee extension, fractured	18	50 (7; 73)	-20; 140
Knee extension, non-fractured	9	23 (14; 38)	-8; 67
Leg press, bilateral	18	38.5 (30; 44)	-38; 78

[a] Different weight training machines were used at the 9 outpatient settings. Accordingly, the percentage progression of loads within the different repetition maximum sessions are reported.
[b] In the first version of the exercise log, it was only possible to register load in knee extension on the fractured leg although both legs were trained during the entire study. This was changed after the first participant, but not all rehabilitation centers succeeded in registering on both legs.

eTable 4: Analysis of secondary outcomes (n=21)							
	Baseline Mean (SD)		**Follow-up Mean (SD)**		**Within-group difference Mean (95% CI)**		**Between-group difference Mean (95% CI)**
Performance	**INT n=11**	**CON n=10**	**INT n=11**	**CON n=10**	**INT n=11**	**CON n=10**	
Handgrip strength (Kg)	27.6 (10.6)	26.8 (5.8)	28.4 (9.7)	26.4 (6.2)	0.9 (-0.9; 2.6)	-0.4 (-2.7; 1.9)	1.3 (-1.4; 4.0)
TUG (s)	27.7 (8.5) [a]	31.4 (14.6)	8.4 (2.2)	8.8 (2.5)	19.5 (14.2; 24.8) [a]	22.6 (12.3; 33.0)	-3.13 (-13.9; 7.7)
10mwt (m/s)	0.63 (0.28)	0.59 (0.25) [b]	1.35 (0.31)	1.33 (0.32)	0.73 (0.58; 0.87)	0.72 (0.38; 1.06)	0.004 (-0.35; 0.35)
DEMMI (0-100)	45.2 (6.8)	44.8 (8.2)	77.4 (11.5)	78.1 (11.4)	32.2 (24.8; 39.6)	33.3 (25.9; 40.7)	-1.1 (-10.9; 8.7)
Patient reported							
NMS (0-9)	8.6 (0.8)	8.5 (1.1)	7.9 (1.3)	8.3 (1.2)	-0.7 (-1.6; 0.1)	-0.2 (-0.7; 0.3)	-0.5 (-1.5; 0.4)
EQ-5D VAS (0-100)	82.7 (17.7)	84.3 (17.9)	82.6 (17.7)	81.5 (12.3)	-0.1 (-10.2; 10.0)	-2.8 (-14.8; 9.2)	2.71 (-11.8; 17.2)
EQ-5D-3L Index Score	0.88 (0.15)	0.90 (0.14)	0.85 (0.14)	0.78 (0.14)	-0.03 (-0.14; 0.08)	-0.12 (-0.22; -0.01)	0.08 (-0.06; 0.23)
Short FES-I (7-24)	12.6 (4.8)	13.9 (4.0)	8.8 (2.5)	8.9 (2.6)	-3.8 (-6.6; -1.0)	-5.0 (-7.0; -3.0)	-1.2 (4.4; -2.1)
Fatigue (0-100)	75.5 (19.7)	67.5 (16.4)	75.0 (24.2)	70.5 (24.1)	-0.5 (-8.5; 7.6)	3.0 (-10.3; 16.3)	-3.45 (-17.6; 10.7)
GDS (0-15)	1.4 (3.3) [b]	1.2 (1.0) [b]	1.9 (4.0) [a]	2.2 (3.1)	0.3 (-0.6; 1.3) [b]	0.1 (-0.5; 0.7) [b]	0.2 (-0.8; 1.2)
MNA-SF (0-14)	13 (1.6)	12.6 (2.3)	12.7 (1.4)	11.7 (2.4)	-0.3 (-1.3; 0.7)	-0.9 (-2.9; 1.1)	0.6 (-1.4; 2.7)
Blood test							
Testosterone, nmol/l	0.66 (0.7)	1.38 (3.1)	5.82 (6.5)	2.75 (5.1)	5.15 (0.90; 9.41)	1.37 (-0.97; 3.71)	3.4 (-0.90; 8.47) [c]
LH, IU/l	11.7 (17.7)	9.2 (8.3)	25.7 (17.3)	28.3 (14.6)	14.0 (0.4; 27.5)	19.1 (9.6; 28.6)	-5.14 (-20.9; 10.6)
FSH, IU/l	24.0 (21.8)	25.4 (13.9)	54.8 (41.0)	56.8 (30.2)	30.8 (14.6; 47.0)	31.3 (16.0; 46.6)	-0.53 (-21.4; 20.4)
SHBG, nmol/l	50.6 (18.6)	72.8 (36.4)	67.0 (36.8)	97.2 (54.7)	16.4 (-4.0; 36.7)	24.3 (-4.7; 53.4)	-7.97 (-40.5; 24.5)
Cholesterol total, mmol/l	3.3 (0.6)	3.4 (0.7)	5.2 (1.0)	4.8 (1.0)	1.9 (1.2; 2.6)	1.4 (0.8; 2.1)	0.47 (-0.39; 1.33)
HDL, mmol/l	1.2 (0.3)	1.2 (0.5)	1.6 (0.5)	1.8 (0.7)	0.4 (0.2; 0.8)	0.6 (0.4; 0.8)	-0.18 (-0.49; 0.12)
LDL, mmol/l	1.4 (0.5)	1.4 (0.7)	2.7 (1.2) [a]	2.3 (0.9)	1.2 (0.5; 2.0)	0.9 (0.4; 1.4)	0.37 (-0.44; 1.18)
Triglycerid, mmol/l	1.52 (0.27)	1.72 (0.48)	2.08 (1.24)	1.60 (0.75)	0.56 (-0.17; 1.30)	-0.12 (-0.49; 0.24)	0.69 (-0.10; 1.47) [d]
CRP, mg/l	143.1 (102.9)	91.5 (47.1)	7.7 (11.3)	2.8 (3.9)	-135.4 (-202.0; -68.7)	-88.7 (122.8; -54.6)	-46.7 (-118.2; 24.9)
Body composition							
Weight, kg	75.9 (12.1)	74.6 (16.7)	71.9 (11.8)	72.3 (16.9)	-3.9 (-6.2; -1.6)	-2.3 (-4.2; -0.3)	-1.66 (-4.50; 1.19)
BMI	27.5 (4.4)	25.8 (5.0)	26.0 (3.8)	25.2 (5.0)	-1.4 (-2.4; -0.5)	-0.6 (-1.4; 0.2)	-0.83 (-1.97; 0.31)

BMD total, g/cm2	1.20 (0.10)	1.16 (0.16)	1.22 (0.11)	1.15 (0.13)	0.019 (0.001; 0.037)	-0.015 (-0.055; 0.025)	0.034 (-0.008; 0.076)
LBM total, kg	47.2 (9.4)	47.4 (10.6)	45.2 (8.9)	44.1 (10.3)	-2.0 (-3.5; -0.5)	-3.3 (-4.3; -2.3)	1.3 (-0.44; 2.97)
LBM right arm, kg	2.2 (0.6)	2.3 (0.8)	2.3 (0.6)	2.3 (0.9)	0.1 (-0.1; 0.2)	0 (-0.1; 0.1)	0.1 (-0.10; 0.29)
LBM left arm, kg	2.0 (0.6)	2.1 (0.8)	2.2 (0.7)	2.1 (0.7)	0.2 (0.1; 0.4)	0.01 (-0.2; 0.2)	0.2 (-0.01; 0.42)
LBM fract. leg, kg	8.5 (2.1)	8.4 (2.0)	7.0 (1.5)	6.7 (1.7)	-1.5 (-2.2; -0.8)	-1.7 (-2.1; -1.2)	0.12 (-0.67; 0.91)
LBM non-fract.leg, kg	7.0 (1.8)	7.0 (1.6)	7.0 (1.5)	6.8 (1.7)	0.01 (-0.3; 0.3)	-0.2 (-0.5; 0.1)	0.17 (-0.25; 0.59)
LBM summed upper extr.	4.2 (1.2)	4.4 (1.6)	4.5 (1.3)	4.4 (1.5)	0.31 (0.05; 0.57)	0.01 (-0.30; 0.32)	0.30 (-0.07;0.67)
Fat mass	26.5 (8.9)	27.0 (8.5)	25.2 (7.8)	27.1 (8.6)	-1.3 (-2.6; 0.04)	0.1 (-1.1; 1.3)	-1.37 (-3.03; 0.29)

Note. TUG: Timed Up and Go test, 10mwt: 10 meter walk test, DEMMI: de Mortons Mobility Index, NMS: New Mobility Score; EQ-5D: EuroQol- 5 Domain, VRS: Verbal rating scale, Short FES-I: Short Falls Efficacy Scale-International; GDS: Geriatric Depression Scale, MNA-SF: Mini Nutritional Assessment Short Form, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, SHBG: Sex hormone binding globulin, HDL: High density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol, CRP: C-reactive protein. BMI: Body Mass Index, BMD: Bone Mineral Density, LBM: Lean body Mass.
Note. For between group differences T-test or Wilcoxon ranked sum test have been performed according to our best evaluation of normal distribution.
[a] n=10
[b] n=9
[c] Data is not normally distributed and a non-parametric test (Wilcoxon rank sum, exact) was performed, P=0.04
[d] Satterthwaite due to unequal variance

eTable 5: Physical activity (Active Pal, measured at week 12, after ceased intervention)

	Intervention (n=10) [a] Mean (SD)	Control (n=10) Mean (SD)	Difference Mean (95% CL)
Sedentary time, hours/day	18.3 (2.9)	19.0 (0.9)	-0.68 (-2.78; 1.42) [b c]
Upright time, hours/day	5.7 (2.9)	5.0 (0.9)	0.68 (-1.42; 2.79) [b]
Steps/day	5952 (4673)	6071 (2777)	-119 (-3731; 3492) [d]
Transfers/ day	45.9 (15.4)	45.1 (8.6)	0.78 (-10.9; 12.5)

Note. Measured over 7 days (4 patients only 6 days, due to battery issues, and one patient only 2 days due to allergic reaction caused by the patch fixating the monitor).
[a] 1 missing due to Covid-19
[b] Satterthwaite due to unequal variance
[c] Minus indicate that intervention is less sedentary
[d] Precaution with interpretation due to known problem with Active Pal not recognizing “slow walking” as steps.

eTable 6: Un-related events		
Event	**int**	**con**
Allergy (Quincke's edema)	-	1
Falls	-	3
Treated for Infection cicatrice (different degrees)	2	1
Greenish urine	-	1
Cold (common viral infection)	2	3
Constipation	1	-
Edema primarily operated leg (treated with pressure socks)	2	-
Herpes zoster	1	-
Hip or knee (n=1) related pain	1	5
Myocardial infarction (known coronary stenosis since 2016, medically treated)	1	-
Fainting (hypotension) (same patient)	2	-
Nausea / loss of appetite	-	2
Urinary tract infection	1	1
Recurrence of chronic leg ulcer	-	1
Click sounds from osteosynthesis material	-	1
Feeling depressed (history of depression)	-	1
Dizziness	1	-
Stomach ulcer (history of ulcer), medically treated	1	-
Weight loss (loss of appetite, altered sense of taste had lengthy antibiotic treatment UVI)	-	1
Delayed fracture heeling	1	-
Pressure ulcer heel	1	-
Renal function slightly impaired (preexisting renal impairment)	-	1
Total 39	**17**	**22**

eTable 7: Other blood parameters discussed in text (n=21)							
Outcome	**Baseline**		**Follow-up**		**Within group difference 95% CI**		**Between group diff. 95% CI**
Blood test	***INT***	***CON***	***INT***	***CON***	***INT***	***CON***	
Hemoglobin, mmol/l	6.7 (0.7)	6.6 (0.8)	8.8 (1.0)	8.7 (0.3)	2.1 (1.3;2.9)	2.1 (1.5;2.6)	0.02 (-0.9; 0.9)
Hematocrit, %	0.32 (0.03)	0.33 (0.04)	0.42 (0.05)	0.42 (0.02)	0.10 (0.06;0.13)	0.09 (0.06;0.11)	0.01 (-0.03; 0.05)
Albumin g/L	26.3 (2.8)	25.4 (2.9)	39.2 (3.9)	39.3 (2.5)	12.9 (10.0;15.8)	13.9 (12.0;15.7)	-0.99 (-4.24; 2.27
Note. INT: Intervention group, CON: Control group							

eTable 8: Hip fracture-related pain during muscle strength testing and TUG.																				
	Baseline										**Follow-up**									
	Intervention, VRS 0-4					**Control, VRS 0-4**					**Intervention, VRS 0-4**					**Control, VRS 0-4**				
	0	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Pain (during fractured leg testing), numbers	5	4	1	1	0	4	2	2	2	0	11	0	0	0	0	7	3	0	0	0
Pain (during TUG), numbers	3	4	3	0	0	3	6	1	0	0	11	0	0	0	0	6	4	0	0	0
Note. VRS, Verbal Ranking Scale; 0="no pain," 1="slight pain," 2="moderate pain," 3="severe pain," 4="unbearable pain."																				

Paper 4

“It can’t make things worse” – Older patients’ perspectives on the use of anabolic steroids in rehabilitation following hip fracture: A Qualitative study embedded within a pilot RCT.

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“It can’t make things worse” – Older patients’ perspectives on the use of anabolic steroids in rehabilitation following hip fracture: A Qualitative study embedded within a pilot RCT

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Abstract

Purpose: To explore patient perspectives of participating in a pilot RCT evaluating feasibility and effect of anabolic steroid, physiotherapy and nutritional supplement following hip fracture.

Methods: Semi-structured telephone-based interviews of 16 women and 3 men (average age 73 years) were conducted at baseline and after a 12-week intervention. Qualitative content analysis was performed.

Results: Two main categories were identified: 1) *Trust and hope for a positive change* with three sub-categories; Reflections on anabolic steroids, Anticipation of extra attention, Lack of energy. 2) *Curiosity, care and commitment* with four sub-categories; A sense of anabolic steroids, Feeling of exclusivity and privileges, Challenges and sense of obligation, and Perspectives on personal gain.

Conclusion: Findings suggest high acceptability of the intervention. Participants motivated their participation on a trust that the intervention would 'do more good than harm'. They found the randomization and possibility of receiving anabolic steroids intriguing, and especially valued trial participation because of their experience of getting extra care and 'deluxe' rehabilitation including close contact and support by health professionals. Our findings may help inform future research recruiting older patients and generally considered relevant for health professionals in rehabilitation, emphasizing the impact of professional guidance and social support to encourage self-efficacy.

Keywords (5-8): Hip fracture, Anabolic steroids, Rehabilitation, Strength training, Motivation, Acceptability, Physiotherapy, Older patients

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Introduction

Sustaining a hip fracture is a common event, and it carries large consequences for the individual such as loss of strength [1–5] and function, decreased quality of life, increased need for help and public services, and an increased risk of further fractures and death [6,7]. As such, hip fractures pose a substantial economic challenge for the health care system [8].

Regaining function and independent mobility after a hip fracture is therefore essential and is considered the primary goal of hip fracture rehabilitation. Rehabilitation has the potential to improve mobility and muscle strength following hip fracture [9], nonetheless previous research shows that up to 50% of patients do not regain pre-fracture function one year post surgery although following an exercise intervention [7,10]. Therefore, further optimization of functional outcome after hip fracture surgery and rehabilitation is of high relevance. Such optimization might be achieved by a multimodal approach adding muscle enhancing medicine to rehabilitation including strength training and nutritional supplements [11–15]. A recent Cochrane Review with few small trials investigating the effect of anabolic steroids in rehabilitation following hip fracture was inconclusive, and further research focusing on the effects, potential side effects and patients' attitudes towards an intervention using anabolic steroids in rehabilitation following hip fracture surgery is warranted [12].

Against this background, we conducted a pilot RCT investigating the feasibility and preliminary effect of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement in patients with hip fracture [16,17]. While acute hospital recruitment proved difficult, adherence to injections and exercise was high indicating high acceptability. Even though sample size was small, promising tendencies were seen for the addition of anabolic steroid on the primary outcome of knee-extension muscle strength [16].

Bearing in mind the complexity of the intervention (i.e. several interacting components), we applied qualitative inquiry alongside the pilot RCT to further explore the patient experience and acceptability of engaging in the composite intervention involving various complex social and behavioral processes and thereby extend findings related to the feasibility aspects of the trial [18,19]. As anabolic steroids are often associated with abuse in athletes, rather than the medical advantages of the drug, we speculated that older patients might be skeptical towards engaging in a trial using anabolic steroids. Additionally, recruitment efficacy declines with increasing age of participants and recruitment of acute hospitalized geriatric populations is known to be challenging [20,21]. Thus, the patients motivation for and acceptability of engaging in a multimodal intervention including anabolic steroids

is of high relevance to inform the findings of the pilot RCT but also in relation to planning future trials and treatment of older patients with hip fracture [19,22].

Thus, the aim of the present study was to explore patient perspectives of participating in a multimodal intervention consisting of anabolic steroid in addition to physiotherapy and protein-rich nutritional supplement following hip fracture.

The following research questions were applied:

1. What motivates older patients with hip fracture to engage in a randomized clinical trial involving anabolic steroids in rehabilitation?
2. How does older patients with hip fracture evaluate their participation in a randomized clinical trial involving anabolic steroids in rehabilitation?

Methods

This qualitative study is reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist [23].

Study design

The current study applied a data-driven, explorative, descriptive design. It was nested within a randomized, blinded, single-center pilot trial which examined the feasibility and preliminary effect of a 12-week multimodal intervention consisting of anabolic steroid in addition to physiotherapy and nutritional supplement on knee-extension strength and function after hip fracture surgery (Clinicaltrials.gov NCT03545347).

Parent Study (and intervention)

A full description of the intervention and results is presented elsewhere [16,17]. Briefly, participants were randomized (1:1) during acute care to: 1. Anabolic steroid (Nandrolone Decanoate) or 2. Placebo (Saline) and received intramuscular injections every 3 weeks. Both groups received identical physiotherapy (with strength training) and a protein-rich nutritional supplement. Participants were referred for physiotherapy in 9 different rehabilitation centers in the catchment area of Copenhagen University Hospital – Hvidovre. They received physiotherapy 1 hour twice a week, up to and including the 12th week after inclusion in the trial. The training session consisted of warm up, functional training, balance training, lower limb exercises and progressive strength training. Two strength training exercises were mandatory (knee-extension and leg press) and performed according to

a standardized progressive protocol. Two daily protein-rich nutritional drinks were offered, containing 18 g milk-based protein pr. bottle (Nestlé Resource 2.0 + fiber).

The participants visited the hospital every 3rd week, where blood tests were carried out, safety parameters assessed, and trial medication administered. They were offered free transportation to both hospital visits and rehabilitation. Throughout the trial, weekly telephone calls were conducted by the project coordinator to ensure and monitor compliance as well as detect potential adverse events.

Participants and setting

Patients admitted to the Hip Fracture Unit, at the Orthopedic Department, Copenhagen University Hospital – Hvidovre were screened for eligibility to enroll in the RCT. Briefly, eligible patients had to be aged 60 or above, pre-fracture home-dwelling, with indoor walking ability and without cognitive dysfunction (disoriented, dementia, delirium). Candidate participants were addressed at the ward 1-4 days post-surgery. Full oral and written information was provided by the project coordinator and participants who agreed to engage in the trial signed an informed consent form [16].
Twenty-nine participants were included in the pilot RCT; four withdrew their consent prior to randomization and two were subsequently excluded prior to randomization due to acute complications. Thus, 23 participants were randomized; 12 were allocated to anabolic steroid and 11 to placebo. Following a consecutive sampling strategy, randomized participants were invited to participate in interviews and describe their experiences. However, the formalities for undertaking interview were first established at the time of including participant ID9. Therefore, only participants from ID9 and onward participated in baseline interviews, while all participants were invited for participation in follow-up interviews.

Data collection

Semistructured telephone-based interviews were conducted at two timepoints. Baseline interviews were conducted 1-2 weeks after enrollment and follow-up interviews within 3 weeks after the participants' trial termination. The project coordinator and first author (SH, female) undertook baseline interviews. SH is a physiotherapist with several years of clinical experience within hip fracture rehabilitation and currently PhD student. SH was familiar with the participants, as she included the participants at the acute ward and performed baseline and follow-up tests according to the pilot-protocol [17]. SH is not trained in interviewing and was supervised by an experienced qualitative researcher (JM). Follow-up interviews were conducted by a second investigator not otherwise involved in the trial (LBL, female). LBL is an occupational therapist by profession, and she

has a master's degree in medical anthropology. She has several years of clinical experience and is responsible for quality and development of occupational therapy at the department and experienced in performing interviews.

Two semistructured interview guides were constructed to guide the interviews. The baseline interview focused on the participants' perspectives in relation to their motivation for engaging in a clinical trial involving anabolic steroids in rehabilitation. Follow-up interviews were focused on the participants' evaluation of their participation in the 12-week intervention, fulfillment of expectations and suggestions for adjustments and consisted of 8 questions (see supplementary files for both interview guides). Few minor adjustments were made to the interview guide after the first couple of interviews. Field notes were made to document content of relevant conversation that was made prior to and after the recording.

Data analysis

The interviews were audio recorded and transcribed verbatim in an anonymized form. Baseline interviews were transcribed by SH and follow-up interviews were transcribed by a trained transcriptionist (samples were checked for accuracy against audio files). Content analysis was performed to develop descriptions of the participants' motivation and evaluation of participation in the trial. A sequential model of deductive and inductive development of categories was undertaken. First, deductive categories based on the study aim and interview guide was applied as a framework in order to structure the content and assist the coding. Secondly, an inductive process of reorganizing categories and establishing new categories was undertaken. All data was read several times by 2 authors (SH and LBL) to get immersed in the data and obtain a sense of the whole [24]. Two authors (SH and LBL) coded all interviews simultaneously and consensus on the coding was reached immediately by discussion. After coding the first 6 interviews (3 baseline and 3 follow-up), a consensus meeting was held with the senior author JM, where codes and process were discussed. Hereafter the remaining interviews were coded and grouped into sub-categories. Sub-categories were generated and refined until all data was classified and hereafter grouped in overarching categories. Investigator triangulation was performed as all four authors participated in a group discussion leading to a final agreement on categories and sub-categories. The analysis process was conducted manually with highlighting meaning units and transferring these to an excel code sheet, and old versions of the code-sheet served as an audit trail.

Results

A total of 19 participants were interviewed (either baseline or follow-up or both). Fourteen baselines interviews were performed and 17 follow-up interviews. The average age of participants was 73 (range: 62-85) years, 16 women and 3 men. Two participants dropped out within the first 2 weeks of the pilot RCT (ID 17 and 21), due to being overwhelmed by the situation after hospital discharge, and they both declined participation in the follow-up assessment and interviews. The last three included participants in the pilot RCT did not complete the planned intervention due to Covid-19, one of them participated in baseline interviews but not follow-up, and the last two participants did not engage in any interviews. Characteristics of the participants included for interviews are displayed in table 1. Baseline interviews lasted for 6-10 min and follow-up interviews from 13-24 min.

Table 1 inserted around here

The analysis resulted in seven sub-categories and two overarching categories related to motivation for enrollment (category 1) and evaluation of participation (category 2), respectively. Categories with sub-categories are depicted in figure 1 and described below supported by participant quotes (written in Italics).

Figure 1 inserted around here

Category 1: Trust and hope for positive change (Motivation for enrollment)

Participants generally described few if any specific expectations towards their engagement in the trial. Minor concerns were overruled by anticipation of benefits from extra attention and an overall trust - tending blind faith, in the aim of the study and the study staff.

Reflection on anabolic steroids

Participants generally expressed little knowledge of anabolic steroids and stated that anabolic steroids were not something they were particularly preoccupied with and not really a cause of concern. Some had never heard of anabolic steroids prior to entering the trial, while others were acquainted with the term and linked it to illegal abuse and bodybuilding. They generally referred to it with a degree of humor and used caricatured images such as ‘bloated’, ‘inflated pool toy’ and ‘bulging out’ to describe their knowledge.

“The only thing I know of, is that you gain more muscle and become bulkier (laughter). I am not aware of anything else, other than you may abuse it”. (ID16)

Largely, participants were not skeptical or worried toward engaging in a study involving the use of anabolic steroids. Few mentioned the potential side effects, but they perceived the risk to be negligible

and temporary. Their worries were overruled by a general trust related to the project and they felt in safe hands. They recounted relying on the study staff and health professionals, being experts and wanting the best for them. They expressed that they didn't feel they had anything to risk, as they always had the opportunity to discontinue. Further, they anticipated that they would benefit from the extra attention and hospital controls which they argued overruled the potential risks.
"What the heck, it can't make things worse, than it is, it can only make it better, I thought". (ID15)

While some decided on trial participation themselves, others were urged by relatives. Generally, participants described their relatives as being supportive of their engagement in the trial. However, one participant described her son being a little skeptical towards her not knowing, what was in the injection, and if it could be of risk to her.

Anticipation of extra attention

Asked directly of their expectations for engaging the trial most participants didn't really have that many expectations and few directly expressed that they did not really remember. Some joined the trial purely for altruistic reasons, and they were driven by a desire to help science and future generations. Furthermore. participants highlighted randomization as an exciting factor, not knowing if they were getting the 'real thing' or placebo.
A major motivational factor for entering the trial was the opportunity to be monitored more closely and get extra hospital controls throughout the course of the trial, which, according to participants, provided them with a most welcome feeling of being taken care of and in safe hands during a time of insecurity. *"You'll keep an eye on me. You don't just leave me to myself, it's something extra". (ID24)*

While time spend on trial participation was an issue for some prior to enrollment e.g. going to the hospital every 3 weeks, and perceived as a drawback, most participants expressed that they had plenty of time but emphasized, that getting free transportation was essential for their participation.

Overall, participants expressed a hope and opportunity that engaging in the trial might lead to a faster recovery and regain of strength and thereby returning to a normal life as before the fracture. Further, one participant described, how he/she was excited about the exercise intervention including the extra focus on strength training, which he/she perceived as a welcome challenge and motivational for engaging in the trial.

Lack of energy

Even though they agreed to participate (i.e. signed informed consent), some participants described doubt and barriers for entering the trial. They expressed a feeling of being distressed and a total lack of energy at the time of information and inclusion, and they had doubts concerning, if they would have the energy to participate. *"I was not really in the mood for anything at the time /…/ it was an uphill battle, I think – the whole thing". (ID21)*

Retrospectively, some expressed the feeling of being groggy from medication at the time of trial information (1-4 days post-surgery) and that they were not fully able to comprehend the extensive information provided. However, most described feeling well informed about the trial and procedures, and they appreciated, that they were given time to consider and discuss participation with relatives.

Category 2: Curiosity, care and commitment (Evaluation of trial participation)

Participants expressed curiosity, excitement and bodily sensations in regard to the possibility that they had received anabolic steroids. They perceived themselves as being privileged trial participants with the notion and gratitude of getting the "deluxe-model" including additional attention and care provided by trial staff. Moreover, they valued the challenging exercises and recounted feeling committed to the trial.

A sense of anabolic steroids

Participants expressed a great interest and curiosity about their allocation and if they had received the anabolic steroid or the placebo injections. Many had a clear feeling of either anabolic or placebo based on bodily changes or sensations. Participants that were convinced, they were getting anabolic steroid related it to hot flushes, nausea, weight gain, getting a rash, increased libido and muscle soreness. Some had turned to the written information about potential side effects, which they expressed confirmed their feeling of getting anabolic steroid, but at the same time they expressed an awareness of a potential placebo effect. Others came to the conclusion, that they had gotten placebo, as they didn't feel "a thing" from the injection site, and a male participant claimed that he "did not feel more masculine". Participants experiencing adverse events that they speculated potentially could be related to the anabolic steroid downplayed it, as of minor importance and instead highlighted the positive experiences of participation in the trial.

"I wonder if there was something in it". Well, I noticed, when I was almost done taking these (injections), *that my hair had started to grow a tad bit too much around the mouth. But you know what? I don't think that it's right. I think that it would have been there anyway (laughter)". (ID14)*

Feeling of exclusivity and privileges

Participants expressed a general feeling of getting something extra that they would not have been offered or have access to, if not participating in the trial – i.e. that participating in the trial gave access to extra privileges. Participants expressed great appreciation of the additional hospital controls, as they felt thoroughly checked and reassured. Further, some expressed gratefulness since the extra examinations led to discovery of previous unknown conditions (i.e. hypertension, osteoporosis), which provided an opportunity to initiate early treatment. Additionally, they expressed enthusiasm about being monitored closely, as it allowed them to follow their recovery process and provided new insights of their body and health, which was perceived as a motivational and retaining factor during the trial. This applied both to the hospital assessments, but also to a great extend to the structured and progressive strength training exercises providing participants with a session to session status of their progress.

Participants stressed the importance of the close relation with the project coordinator that developed during the course of the trial. They appreciated the weekly phone calls and that someone showed interest in their well-being. The project coordinator was an accessible health professional, that participants could direct their concerns and worries to, and she was perceived as a source of information and a link to both doctors and the physiotherapists in the municipality. Further, participants stressed the importance of their various hospital visits being coordinated, which helped them create an overview and offered security. Participants described how the project coordinator provided encouragement and emotional support, which offered a feeling of comfort and being in good hands.

"P: I kind of like being pampered. This is another form of pampering, right?

I: Yes, a little extra attention you mean?

P: Yes, I think we all like that." (ID24)

In relation to the municipality-based physiotherapy intervention, some participants expressed that they were given extra attention by getting additional and what they perceived to be more effective training based on the notion that they performed individually supervised strength exercise and not merely the standard group exercises offered to peer patients with hip fracture not involved in the trial.

"That usual form of hip training, where you walk around with an elastic band and that kind of thing, that I didn't care much for…, well, I might as well do that at home. But the strength training we received – us who participated in the project and which the others in the group didn't receive, I would say that was really good!" (ID19)

Challenges and sense of obligation

All participants valued the strength exercises, only one participant expressed that she missed more time spent on flexibility exercises, as the strength exercises were time-consuming. Several recognized the strength training as being the active ingredient effective in accelerating the recovery process and enhancing the regain of muscle strength. Generally, they perceived the strength training as strenuous and hard pushing them to the limit, but at the same time it was perceived as necessary and beneficial. Some participants expressed that it was equal parts carrot and stick. Some associated the strength exercise with pain, which for some were unpleasant but for others was perceived as a natural consequence of exercise.

The exercise being supervised was motivating and participants recounted feeling obligated to engage as someone was expecting them, which helped them get out the door. The physiotherapists were viewed as experts giving directions, appropriate challenge and cheering, which felt reassuring and encouraged them to perform beyond what they thought possible.

"It (strength training) *has been really good, because you kind of, I won't say outdo yourself, but you just put more effort into it, right? I thought: I can do it, I can do it, I can do it!" (ID19)*

On the other hand, it was also articulated that the group session had value, as participants could compare themselves to others.

The same feeling of commitment was expressed in relation to the intake of the protein-rich nutritional supplement. Many participants disliked the drinks and consuming two bottles a day was perceived as a considerable challenge. Generally, they felt guilty about not being able to consume the drinks, as they had committed to the trial, and really wanted to live up to this commitment. Some of them recalled trying to compensate by eating more eggs or by buying other protein-rich products at the supermarket.

"Because, I felt that once I had committed, I had a certain obligation to do, what we had agreed on. But it tasted so awful, that I couldn't drink it, and I was really sad to tell." (ID24)

On the contrary, some appreciated that the drinks were provided for free, others liked the accessibility, especially during the first weeks, where preparing a proper meal was difficult. Few expressed they enjoyed the drinks and hoped that it would help them regain their strength faster.

The free transportation to and from the hospital and rehabilitation centers in the municipality was crucial for trial participation, but they also expressed that the offered transportation was associated

with inconvenient waiting time. Also, participating in the study was by some perceived as time-consuming and interfering with other plans or activities. Nonetheless, participants described a whole heartedly engagement in the trial. "*Once I have committed to something, I will go for it 100%." (ID13)*

Perspectives on personal gain

Participants' personal outlook might have influenced how they felt and acted during the trial. Many participants expressed being aware of the importance of keeping active in daily life, walking, doing home exercises and trying to resume their usual activities. In daily life they tried to challenge themselves, pushing themselves out of their comfort zone. They endeavored and put an honor in being independent. *"You do not get well through the mail, right?" (ID3)*

All participants described a feeling of progress and getting better during the course of the trial. While some were surprised how fast the pain diminished and they recovered mobility, others had expected a faster recovery and still struggled with limping and pain.

Generally, participants associated their good outcome to trial participation. Some felt it was the effective exercise that was the explanatory factor of their fast recovery, while others felt the injections must have boosted the positive outcome.

"It (trial participation) *has helped me recover so quickly, or at least I assume it has, because I have talked to someone who hasn't participated in the project, and they were rather miserable to look at compared to me (laughter). I am after all 77* (years old). *I'm not the youngest model." (ID16)*

Accordingly, several participants wished that the trial had run a bit longer for the sake of maintaining the exercise, as they anticipated, that it would be harder to motivate themself to exercise after trial completion. Likewise, some participants described, that they by own initiative had signed up for exercise groups or continued exercising on their own after trial completion.

Unanimously, participants stated that they would recommend others to participate in a similar trial. Some with the motive of helping science others because of the exercise and the "extra" privileges provided. Their recommendations were however often conditioned by potential new participants should be aware of the extra time that trial participation acquired.

"Yes, I definitely would (recommend participation). *I would! I think it is something you should agree to, because you get so much more, than if you just have the operation and go straight home, right? So definitely I would." (ID9)*

Discussion

The purpose of this qualitative study was to gain understanding of older patients' experiences of engaging in a complex intervention including anabolic steroids in rehabilitation after hip fracture. Overall, at baseline, participants were somewhat Carefree and untalkative in relation to their expectations towards engaging in the trial; they based their motivation for enrollment on a trust that the intervention would 'do more good than harm'. At follow-up, they had a very positive perception of participating in the trial, as they felt well taken care of, including extra attention from health professionals. They explained being curious about the possibility of having received anabolic steroid and appreciated the access to a more intensive exercise program. Particularly, the individualized and progressive strength training was highlighted by many, as the key ingredient for their recovery. Further, participants felt committed to the trial putting an effort in to adhering to trial elements.

Our preconception was, that patients would be reluctant towards engaging in a trial using anabolic steroids in rehabilitation, since harmful consequences of the abuse of anabolic steroids in athletes and in fitness environments has been covered largely in the media. Surprisingly, this was not a major concern for the participants, and they generally expressed limited knowledge about anabolic steroid. The interviewed participants' views are in line with the eligible patients who declined to participate in the pilot trial, for whom worries of anabolic steroid was also not a major concern [16].
For those participants that did express some concern, these were outweighed by a substantial faith in the study staff wanting the best for them, and additionally the anticipated potential gains from participating in the trial. It has previously been established that self-efficacy, which is essential to engaging in new health behavior, are reinforced by incentives from trusted health authorities through verbal persuasion and encouragement [25]. This highlights the importance of establishing a friendly and trustful relation and providing thorough, understandable information to enhance inclusion of older patients in clinical trials, which is also emphasized in previous studies [26,27]. Additionally, health professionals might be perceived as epistemic authorities [28] and as such the deference to authority might serve as a decision-making shortcut.

Another factor that might have influenced trial recruitment, was that participants were approached and informed just 1-2 days after surgery. At this point some participants described being distressed and lacking energy, which is in accordance with the main reason for eligible patients to decline participation in the pilot trial (37% were feeling overwhelmed by the situation) [16]. This reason for

declining participation is also supported by other studies, where hip fracture patients during the acute hospital stay describe feelings off vulnerability, hopelessness and being concerned with how to manage at home [29–31]. Patients describe suffering a hip fracture as a life breaking event [30,32], and it could raise concerns of how much trial information, the participants can actually take in during acute hospitalization. In line with our findings, a previous study by Asplin and colleagues [29] indicate, that there were variations in the patients ability to remember and process information during the acute phase. This highlights the importance of keeping information simple, but also illustrates the paradox between the rising amount of formalities having to be included in participant information for it to live up to authority rules, and what is actual possible for patients in crisis to process. Moreover, our finding that some participants accepted inclusion, because they believed that things could not be worse (i.e. that their participation could only improve their condition), indicate that some patients may have been in a state of despair, but also that trial participation for some may provide hope, and that participants valued the opportunity to get something "extra" in this time of insecurity. Their ability to remember and process information might also be reflected in the short baseline interviews; although the baseline interview took place just 1-2 weeks after enrollment, participants recounted not remembering or not really having any expectations for enrollment.

The close contact to the project coordinator including weekly phone calls and hospital visits every 3 weeks, was emphasized as a major benefit of participation, influencing the participants' overall positive evaluation of trial participation. The trustful relation to the project coordinator/staff was perceived as a source of support and motivation throughout the course of the trial. Previous research exploring hip fracture patients experiences during the rehabilitation phase also highlights the importance of support, information and encouragement from health care professionals [33,34]. Health professionals are perceived as experts knowing the recovery process and providing relevant information making patients feeling reassured [34], and their encouragement might impact on the patients feeling of self-efficacy [35,36] . In the current study the project coordinator's ongoing involvement and feedback to the participants in relation to their recovery might also have played a role in modifying (outcome) expectations, which eventually balanced expectations and thereby contributed to satisfaction and appreciation of being enrolled, as supported by the social cognitive theory [36].

Participants generally expressed a positive attitude towards physical activity, acknowledging that recovery demanded an effort. They largely attributed their recovery to the exercise intervention and their willingness to participate and actively engage in the exercises. Their narrations reflected a level

of confidence in their ability to engage in the exercise activities, which could have had a positive impact on adherence and improved outcomes [37]. Opposite of what could be expected from an older patient group recovering from a major trauma, participants expressed high motivation and acceptance of strength training. This could be explained by participants feeling in safe hands and adequately challenged by the physiotherapist, but also the positive demeanor by the physiotherapist cheering and guiding them throughout their recovery [38,39].

The participants greatly appreciated being monitored and receiving the extra information on their health and recovery progress. This applied both to the hospital visits but also to the structured strength training allowing them to follow their progress from time to time. The quantitative findings suggested a low starting point for especially the fractured leg strength, which resulted in noticeable increases in strength within the first sessions [16]. This might have provided a feeling of success and regaining previous self, that have fueled self-efficacy, especially considering that this success was achieved in the face of challenge, being impaired and experiencing pain [36]. Participants stressed the importance of supervision to maintain motivation and adequate challenge, which is in accordance with previous findings, where patients expressed lack of motivation for unsupervised home-exercise programs [33], as such the supervision in the present study might have been a contributing factor for the high adherence to the exercise intervention (91%) [16]. The participants' statements are supported by existing evidence indicating larger effect sizes for supervised exercise intervention compared to non-supervised interventions [9,40,41]. Further, the high adherence rate indicates that elements of the intervention has supported self-determination (the participants feeling of autonomy, competence and relatedness) fundamental for retention to a health intervention [42]. Additionally, the high acceptance of the exercise component is also reflected in the participants' wish to continue to exercise after trial completion, which further supports that the intervention promoted self-efficacy and self-determination.

Methodological considerations

This study has strengths and weaknesses. To evaluate trustworthiness of the trial we consider the components of credibility, transferability, confirmability and dependability [43]. Credibility was addressed in part by including quotes directly from participants to demonstrate representativeness of the original data, but also by a circular analysis process assuring, that the categories were rooted in the original data. It is considered a strength, that all available/potential participants were approached and agreed to take part in interviews. Unfortunately, the two participants dropping out from the pilot RCT were not interested in being interviewed, and therefore their perspectives are not reflected in the data. The participants included in the pilot RCT were younger and better functioning than the usual

population of older patients with hip fracture [44], therefore findings cannot directly be transferred to contexts involving older and more impaired patients.

Also, credibility and confirmability were supported through triangulation reducing the potential effect of investigator bias. The current analysis was performed by investigators having different professional and scientific backgrounds. All coding was conducted by 2 authors but with a sub-sample of 6 transcripts coded by 3 authors. Debriefing sessions by the group of authors were conducted throughout the analysis process providing the opportunity to test ideas and interpretations. This also aided saturation as we were several people involved in making sure that the final analysis represented all the emerged codes and categories [45]. We have attempted to describe the analysis process as accurate as possible and used the COREQ checklist [23] in order to heighten dependability and confirmability.

Conducting telephone interviewing was feasible and acceptable for participants, but we can't exclude the possibility, that face-to-face interviews would have provided further reflections on the subject, and an opportunity for the interviewer to assess and validate the participants' experiences by taking body language into account. The baseline interviews were very short, which in part could be due to the participants not having many expectations entering the pilot RCT, but the interviewers lack of experience might also have been an influencing factor. The interviewer performing baseline interviews, was also the project coordinator and experienced difficulties sticking to the role as interviewer not trying to explain project details etc. Thus, it cannot be ruled out that involvement of an interviewer not otherwise involved in the project and/or interview of spouses/relatives would have resulted in more thick descriptions regarding motivation for enrollment. However, participants appreciated being approached by someone they felt they knew, and who they perceived as a clinical expert.

Social desirability bias could be a limitation, but we tried to circumvent this factor, with the interviewer conducting follow-up interviews not being otherwise involved in the trial; additionally, we emphasized that all opinions (negative and positive) were valued. Also, the emerging categories of this study were supported by similar findings in studies exploring older adults' recovery from hip fracture which adds to the credibility of our findings.

Conclusion

Our study captured older patients' experiences of engaging in a trial using anabolic steroids in addition to physiotherapy and protein-rich nutrition supplement in rehabilitation after hip fracture. Our findings suggest high acceptability of the intervention, and contrary to our expectations, participants found the randomization and possibility of receiving anabolic steroids intriguing. Trial participation

was highly valued because of what participants perceived to be extra care/deluxe rehabilitation including close contact with and support of health professionals. Especially the individualized and structured progressive strength training was highly valued, and considered a key component for recovery, by participants.

Our findings may help inform future trials investigating the effect of muscle enhancing medicine and generally considered relevant for rehabilitation interventions emphasizing the impact of professional guidance and social support in promoting self-efficacy.

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Disclosure statement

The authors state no conflicts of interests

Appendix

File 1: Interview guides

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Table 1: Characteristics of participants

ID	Sex	Age	Interviews A: baseline B: follow-up	Non-cohabit (0) Cohabit (1)	EQ-VAS	NMS
ID 2	F	78	B	1	80	9
ID 3	F	68	B	0	65	7
ID 5	F	69	B	0	100	9
ID 6	F	85	B	0	85	9
ID 7	F	73	B	0	90	9
ID 9	F	73	A+B	1	100	9
ID 10	F	85	A+B	0	50	7
ID 12	F	66	A+B	0	93	9
ID 13	M	77	A+B	0	90	9
ID 14	F	83	A+B	0	60	6
ID 15	M	73	A+B	1	95	9
ID 16	F	76	A+B	0	85	9
ID 18	F	65	A+B	1	97	9
ID 19	F	65	A+B	1	70	9
ID 20	F	74	A+B	1	98	9
ID 21	F	72	A	0	90	9
ID 22	M	62	A+B	1	95	9
ID 24	F	73	A+B	1	100	9
ID26	F	66	A	0	90	9

Start interviews were first initiated by the time ID 9 was included.
ID 1,4,11,23,25,29 dropped out prior to randomization and therefore not displayed.
ID 8 Follow-up interview lost when transferring datafile from recorder to computer
ID 17 dropped out and no interviews were conducted. ID 21 dropped out after baseline interview.
ID26 No follow-up interview due to large deviation from intervention caused by Covid-19
ID 27, 28 Neither baseline nor follow-up interviews conducted due to large deviation from intervention caused by 1st Covid-19 wave.
Pre-fracture EQ-VAS: European Quality of Life – visual analogue scale (range 0-100), higher scores indicate better health status.
Pre-fracture function - NMS: New Mobility Score (range 0-9), score=9 indicate independent walking indoor, outdoor and during shopping.

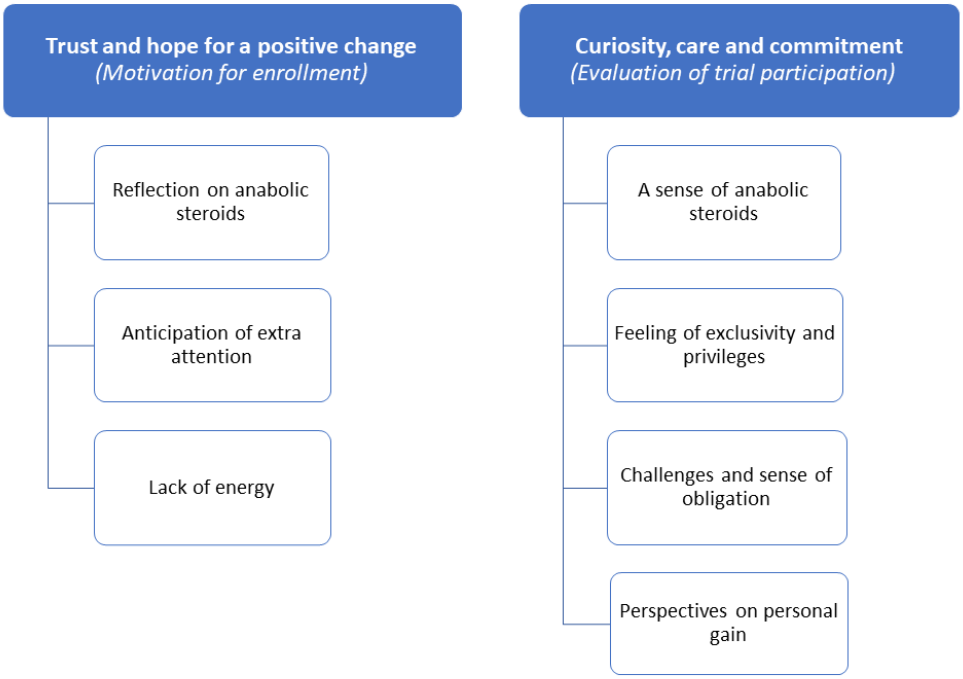

Figure 1: Overview of categories and sub-categories.

Appendix

Semi-structured Interview guides

Baseline Interview

Introduction	• Presentation of interviewer /purpose • Confidentiality • The structure/frame of the interview session • Questions before start?
Main interview questions	What considerations did you have about accepting to participate in the project? - Can you tell a little about what made you want to participate in the project? (+/-) - Is there anything / anyone who has influenced your decision? - Which elements of the project do you find the most interesting / exciting?
	What do you hope to obtain from participating in the project? - What do you see as benefits/drawbacks of participation?
	Do you have any worries concerning your participation?
	Have you heard of anabolic steroid prior to this project? - What do you know of the effect of anabolic steroid? - Has it influenced on your decision to participate?
Closing	Is there anything you would like to add before we finish off?

Follow-up Interview

Introduction	• Presentation of interviewer /purpose • Confidentiality • The structure/frame of the interview session • Questions before start?
Main interview questions	What do you consider the best part about participating in the trial? - Can you say a little more about why exactly that, was the best thing about participating?
	What was the hardest or worse part about participating? - Can you say a little more about why that, was the hardest thing about participating?
	Do you feel that there is something that made a special impression / or surprised you during the trial participation? - Or was different from what you expected?

	Have your expectations to be part of the project been met?
	Could we have done something different or better?
	Would you recommend others in the same situation as you to participate in the trial? And is there anything they should be aware of / pay attention to?
	How have your relatives reacted to your participation in the project?
	Do you have any feeling/ idea about if you have got the placebo or anabolic steroid?
Closing	Is there anything you would like to add before we finish off?

Examples of clarifying questions:

Can you tell more about that?

Con you give examples of that?

When you say…, do you mean..?