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Clinical Research Centre;
Physical Medicine & Rehabilitation Research – Copenhagen (PMR-C);
and Clinical Orthopedic Research Hvidovre (CORH), Department of Orthopedic Surgery,
Copenhagen University Hospital, Hvidovre

PhD thesis

Rasmus Skov Husted

Coordinated exercise and surgical care of patients with knee osteoarthritis who are eligible for knee replacement: A pragmatic approach (The PREHAB-KR project)

Dose-response relationship of pre-operative knee-extensor exercise in patients eligible for knee replacement

Supervisor: Thomas Bandholm

Co-supervisors: Anders Troelsen and Michael Skovdal Rathleff

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Copenhagen University Hospital, Hvidovre
Kettegaard Allé 30
DK-2650 Hvidovre, Denmark

UNIVERSITY OF COPENHAGEN

Author:	Rasmus Skov Husted
Name of department:	Clinical Research Centre, Copenhagen University Hospital, Hvidovre
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Principal supervisor:	**Thomas Bandholm**, PhD, Professor. Clinical Research Centre; Physical Medicine & Rehabilitation Research – Copenhagen (PMR-C); Department of Physical and Occupational Therapy; Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Amager and Hvidovre, Denmark
Co-supervisors:	**Anders Troelsen**, PhD, Professor, Clinical Orthopedic Research Hvidovre (CORH), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Amager and Hvidovre, Denmark
	Michael Skovdal Rathleff, PhD, Professor, Center for General Practice at Aalborg University; Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark
Assessment Committee:	
Chairman:	**Marius Henriksen**, Professor, Department of Clinical Medicine, University of Copenhagen, Denmark
Opponents:	**Henrik Schrøder**, Associate Professor, University of Southern Denmark, Denmark
	Karen Barker, Professor, University of Oxford, United Kingdom

Contact information:

Rasmus Skov Husted
Clinical Research Centre (Section 056)
Hvidovre Hospital, University of Copenhagen
Kettegaard Allé 30
DK-2650 Hvidovre, Denmark
E-mail: rasmus.skov.husted@regionh.dk
Orcid: 0000-0003-2020-8792

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List of papers and manuscripts included in the PhD thesis

Study I
Husted RS, *Juhl C, Troelsen A, Thorborg K, Kallemose T, Rathleff MR, Bandholm T.* The relationship between pre-operative knee-extensor exercise dose and change in knee-extensor strength prior to and following total knee arthroplasty: A systematic review and meta-regression analysis of randomized controlled trials. In revision at *Osteoarthritis and Cartilage*. Submitted 25th October 2019.

Study II
Husted RS, *Troelsen A, Thorborg K, Rathleff M, Husted H and Bandholm T.* Efficacy of pre-operative quadriceps strength training on knee-extensor strength before and shortly following total knee arthroplasty: Protocol for a randomized, dose-response trial (The QUADX-1 trial). 2018. Published in *Trials* (Open Access).

Study IV
Husted RS, *Bandholm T, Troelsen A, Kirk J.* Perceived facilitators and barriers among physiotherapists and orthopedic surgeons to pre-operative home-based exercise therapy with *one* exercise-only in patients with severe knee osteoarthritis: A qualitative interview study nested in the QUADX-1 trial. Submitted to *PLOS ONE* 27th January 2020. Open access preprint available at medRxiv.org. Doi: 10.1101/2020.01.22.20018416.

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The following papers and work are not included in the thesis but reflects additional work done while being a PhD student.

Accepted peer review publications

- *Ishøi L, Krommes KK, **Husted RS**, Juhl C, Thorborg K.* Diagnosis, prevention, and treatment of common lower extremity muscle injuries in sport – grading the evidence: a statement paper commissioned by the Danish Society of Sports Physical Therapy (DSSF). 2020. British Journal of Sports Medicine.

- *Kirk JW, Bodilsen AC, Sivertsen DM, **Husted RS** and Thørnhøj-Thomsen* T. Disentangling the complexity of mobilization of older medical patients in routine practice: An ethnographic study in Denmark. 2019. PLOS ONE.

- ***Husted RS***. Diagnosis, prevention and treatment of acute lateral ankle sprains. 2019. Ugeskrift for Laeger.

- *Bandholm T, **Husted RS**, Jakobsen TL.* Letter to the editor regarding "Is it necessary to perform prehabilitation exercise for patients undergoing total knee arthroplasty: meta-analysis of randomized controlled trials". 2018. The Physician and Sportsmedicine.

- *Kirk JW, Bodilsen AC, Thørnhøj-Thomsen T, Pedersen MM, Bandholm T, **Husted RS**, Kronborg L, Petersen J, Andersen O and Nilsen P.* A tailored strategy for designing the WALK-Copenhagen intervention to increase mobility in hospitalized elderly medical patients: a protocol for the qualitative part of the WALK-Copenhagen project. 2018. British Medical Journal Open (Open Access).

- ***Husted RS**, Bencke J, Hölmich P, Andersen LL, Thorborg K, Bandholm T, Jakobsen BG, Lauridsen HB, Myklebust G, Aagaard P and Zebis MK.* Maximal lower extremity muscle strength is unrelated to neuromuscular activity obtained during a movement associated with non-contact ACL injury: A cross-sectional study. 2018. International Journal of Sports Physical Therapy.

- ***Husted RS****, *Wilquin L*, Jakobsen TL, Holsgaard-Larsen A and Bandholm T.* Rapid knee-extensions to increase quadriceps muscle activity in patients with total knee arthroplasty: A randomized cross-over study. *Shared first authorship. 2017. International Journal of Sports Physical Therapy.

Other work

- Three months research stay abroad in Dunedin, New Zealand at the School of Physiotherapy, University of Otago. Co-working on two projects related to exercise therapy and knee OA and initiation of collaboration for drafting below protocol.
- Drafting protocol for the systematic review "*Trial registration and reporting characteristics of trials investigating exercise-based rehabilitation following total knee arthroplasty: A systematic review*". Pre-registered protocol available here https://osf.io/6wzre.
- Co-supervised one MSc students master thesis.
- Co-writing eLetter to the editor, available here https://bit.ly/371dIcU.

Summary in English

Coordinated exercise and surgical care of patients with knee osteoarthritis who are eligible for knee replacement: A pragmatic approach (The PREHAB-KR project)

Patients with knee osteoarthritis (OA) suffer from knee pain, a decrease in physical function and quality of life. If the knee OA condition progresses, the patients eventually become eligible for knee replacement to overcome their symptoms. However, international guidelines recommend that non-surgical treatment (e.g. exercise) is tried out before surgical treatment is considered. Physically, the main characteristic of patients with knee OA is decreased knee-extensor muscle strength which is associated with knee OA progression and worsening of symptoms. Following surgery, knee-extensor strength is further decreased, potentially prolonging rehabilitation. It is recognized that exercise treatment focusing on knee-extensor strength is important in patients eligible for knee replacement, however, the optimal knee-extensor exercise dosage is unknown.
When new initiatives are investigated in established organizations, e.g. the health care system, it is important to include stakeholder input to identify potential facilitators and barriers to adjust the initiative under study.

The objectives of this PhD thesis were 1) to investigate the knee-extensor dose-response relationship before and after total knee arthroplasty in patients scheduled for surgery (systematic review, study I), 2) to investigate the dose-response relationship of three different home-based knee-extensor exercise dosages of *one* knee-extensor exercise before and after knee replacement in patients eligible for surgery. Further, to investigate this in an intersectoral model of coordinated non-surgical and surgical care (the QUADX-1 trial, study II+III) and 3) to identify perceived facilitators and barriers among physiotherapists and orthopedic surgeons towards coordinated non-surgical and surgical care with *one* home-based exercise in patients eligible for knee replacement (qualitative, study IV).

Study I (systematic review)

Twelve trials with 616 patients were included. Meta-regression analysis showed no relationship between pre-operative knee-extensor exercise dosage and change in knee-extensor strength neither prior to (slope 0.0005 [95%CI -0.007 to 0.008]) or three months following knee replacement (slope 0.0014 [95%CI -0.006 to 0.009]). Before knee replacement, a moderate effect favoring pre-operative exercise for an increase in knee-extensor strength was found (SMD 0.50

[95%CI 0.12 to 0.88]), but not three months after knee replacement (SMD -0.01 [95%CI -0.45 to 0.43]).

Study II+III (QUADX-1 trial)

One-hundred and forty patients eligible for knee replacement were included and randomized to 12 weeks of knee-extensor exercise with either exercise dosage '2 session/week', '4 session/week' or '6 sessions/week'. *The dosages are referred to as group A, B and C as the trial was not unblinded for the thesis*. Assessment of the primary outcome (after exercise) was completed for 117 patients. For the intention-to-treat analysis, 140 patients were included. For the primary outcome *isometric knee-extensor strength* (Nm/kg) no dose-response relationship was observed between the three groups after 12 weeks of exercise – group B vs. A (0.04 [95% CI -0.13 to 0.20], p=0.6685), group C vs. A (0.009 [95% CI -0.15 to 0.17], p=0.9131) and group C vs. B [-0.03 (95% CI -0.18 to 0.13], p=0.7253). For the secondary outcomes, significant differences in change from baseline to after 12 weeks of exercise was found between group C and B for *Oxford Knee Score* (4.2 [95% CI 0.6 to 7.8], p=0.0216) and *average knee pain last week* (NRS 0-10) (-1.1 [95% -2.2 to -0.1], p=0.0303). No between group difference was observed for any other group comparisons or secondary outcomes at the primary end-point. Within group changes showed a positive change for the whole sample and all three groups separately. Larger changes were observed for group C compared to group A and B, and group A compared to group B. Of the 117 patients with assessments after 12 weeks of exercise, 79 (67.5%) postponed surgery, 32 (27.4%) underwent surgery and 6 (5.1%) wanted surgery but this was contraindicated.

Study IV (qualitative)

Four orthopedic surgeons and six physiotherapists were included and interviewed with single- and focus group interviews, respectively. The thematic analysis showed that the pre-operative exercise intervention created ambivalence in the professional role of both the physiotherapists and orthopedic surgeons. The physiotherapists were positive towards supporting patient self-management but skeptical towards a too simplified exercise therapy. The orthopedic surgeons were positive towards having exercise as a treatment option but skeptical towards the potential lack of (long-term) effect of exercise in patients eligible for knee replacement.

Conclusion

In conclusion, results from the systematic review and the QUADX-1 trial show no clear dose-response relationship between pre-operative knee-extensor exercise dosage and change in outcomes before or after surgery in patients eligible for knee replacement. The results indicate that pre-operative knee-extensor strengthening exercise improves outcomes before surgery in patients eligible for knee replacement. Results from the QUADX-1 trial supports the effect of *one* exercise-only knee-extensor exercise before potential surgery in patients eligible for knee replacement with improvement in e.g. the cardinal symptom knee pain. This improvement in outcomes before surgery was independent of prescribed exercise dosage, however there was a tendency for dosage C to be superior to dosage B. In the imbedded qualitative study, we found that the pre-operative *one* exercise-only intervention was associated with barriers creating ambivalence in the professional role of both the physiotherapists and the orthopedic surgeons. These barriers and associated ambivalence in the professional role are important to consider when evaluating the coordinated non-surgical and surgical care pathway.

Summary in Danish/Dansk resumé

Resumé (Summary in Danish)

Koordinering af træning og kirurgisk behandling hos patienter med knæartrose, som er kvalificeret til knæalloplastik: En pragmatisk tilgang (PREHAB-KR projektet)

Patienter med knæartrose lider af knæsmerter, nedsat fysisk funktion og livskvalitet. Hvis knæartrose tilstanden forværres, kan patienterne blive tilbudt knæalloplastik for at fjerne symptomerne. Internationale retningslinjer anbefaler dog, at ikke-kirurgisk behandling (f.eks. træning) afprøves inden kirurgi overvejes. Det største fysiske deficit hos patienter med knæartrose er nedsat muskelstyrke i knæstrækkermusklerne, som er associeret med progression af knæartrose og forværring af symptomer. Efter knæalloplastik er muskelstyrken i knæstrækkermusklerne yderligere nedsat, hvilken kan forlænge rehabilitering. Det er veletableret, at træning af knæstrækkermusklerne er vigtigt hos patienter kvalificeret til knæalloplastik, men den optimale træningsdosis er ukendt.
Når nye initiativer undersøges i veletablerede organisationer som f.eks. sundhedssystemet, er det vigtigt at inkludere holdninger fra interessenter. Dette for at kunne identificere facilitatorer og barrierer til justering af det initiativ som undersøges.

Formålet med studierne i denne Ph.d.-afhandling var 1) at undersøge træningsdosis-responsforholdet for knæstrækkermusklerne før og efter knæalloplastik hos patienter, der var skrevet op til operation (systematisk review, studie I), 2) at undersøge træningsdosis-responsforholdet mellem tre doser af hjemmebaseret knæstrækkertræning med *én* knæstrækkerøvelse hos patienter kvalificeret til knæalloplastik. Dette undersøges i en tværsektoriel model af koordineret ikke-kirurgisk og kirurgisk behandling (QUADX-1 forsøget, studie II+III) og 3) at identificere opfattede facilitatorer og barrierer blandt fysioterapeuter og ortopædkirurger omkring koordineret ikke-kirurgisk og kirurgisk behandling med *én* hjemmebaseret træningsøvelse hos patienter kvalificeret til knæalloplastik (kvalitativt studie, studie IV).

Studie I (systematisk review)

Tolv kliniske studier med 616 patienter blev inkluderet. Meta-regressionsanalysen viste ingen sammenhæng mellem den præ-operative knæstrækkertræningsdosis og ændring i knæstrækkermuskelstyrke hverken før (hældning 0.0005 [95%CI -0.007 to 0.008]) eller tre måneder efter knæalloplastik (slope 0.0014 [95%CI -0.006 to 0.009]). En moderat effekt af præ-operativ

træning på forbedring af knæstrækkermuskelstyrke blev fundet før knæalloplastik (SMD 0.50 [95%CI 0.12 to 0.88]), men ikke tre måneder efter (SMD -0.01 [95%CI -0.45 to 0.43]).

Studie II+III (QUADX-1 forsøget)

Et hundrede og fyrre patienter kvalificeret til knæalloplastik blev inkluderet og tilfældigt tildelt 12 ugers knæstrækkertræning med enten træningsdosis '2 sessioner/ugen', '4 sessioner/ugen' eller '6 sessioner/ugen'. *Doserne bliver refereret til som A, B og C, da forsøget ikke var afblindet til afhandlingen*. Test af det primære outcome, *knæstrækkermuskelstyrke* (Nm/kg), efter 12 ugers træning blev gennemført for 117 patienter. Et hundrede og fyrre patienter var inkluderet i intension-to-treat analysen. Vi fandt intet dosisresponsforhold mellem de tre grupper i *knæstrækkermuskelstyrke* efter 12 ugers træning – gruppe B vs. A (0.04 Nm/kg [95% CI -0.13 to 0.20], p=0.6685), gruppe C vs. A (0.009 Nm/kg [95% CI -0.15 to 0.17], p=0.9131) og gruppe C vs. B (-0.03 Nm/kg [95% CI -0.18 to 0.13], p=0.7253). For de sekundære outcomes fandt vi signifikante ændringer efter 12 ugers træning mellem gruppe C og B for *Oxford Knee Score* (4.2 OKS-points [95% CI 0.6 to 7.8], p=0.0216) og *gennemsnitlig knæsmerte i den sidste uge* (NRS 0-10) (-1.1 NRS-points [95% -2.2 to -0.1], p=0.0303). Vi fandt ikke forskel mellem grupperne på andre sekundære outcomes. Alle tre grupper forbedrede sig efter 12 ugers træning, men vi observerede større ændringer i henholdsvis gruppe C, A og B. Af de 117 patienter der gennemførte de 12 ugers træning valgte 79 (67.5%) at udskyde operation, 32 (27.4%) blev opereret og 6 (5.1%) ønskede operation, men dette var kontraindiceret.

Studie IV (kvalitativt)

Fire ortopædkirurger og seks fysioterapeuter blev inkluderet og interviewet med henholdsvis enkelt- og fokusgruppeinterviews. Den tematiske analyse viste, at den præ-operative træningsintervention skabte ambivalens i den professionelle rolle hos både fysioterapeuter og ortopædkirurger. Fysioterapeuterne var positive omkring at understøtte self-management hos patienterne, men skeptiske overfor en for simplificeret træningsintervention. Ortopædkirurgerne var positive overfor at have træning som en behandlingsmulighed, men skeptiske overfor den potentielle manglende (langtids-) effekt af træning hos patienter kvalificeret til knæalloplastik.

Konklusion

Resultaterne fra det systematisk review og QUADX-1 forsøget viste ikke et tydeligt dosis-responsforhold mellem præ-operativ knæstrækkertræningsdosis og ændring i outcomes hverken før eller efter operation hos patienter kvalificeret til knæalloplastik. Resultaterne indikerer, at præ-operativ knæstrækkertræning forbedrer outcomes før operation hos patienter kvalificeret til knæalloplastik. Resultaterne fra QUADX-1 forsøget understøtter effekten af træning med *én* knæstrækkertræningsøvelse med f.eks. forbedring af kardinalsymptomet knæsmerter. Denne forbedring i præ-operative outcomes var uafhængig af den tildelte træningsdosis – dog var der en tendens til, at gruppe C havde større forbedringer end gruppe B. I det indlejrede kvalitative studie fandt vi, at den præ-operative træning med *én* knæstrækkertræningsøvelse var associeret med barrierer, der skabte ambivalens i den professionelle rolle hos både fysioterapeuter og ortopædkirurger. Disse barrierer og den associerede ambivalens i den professionelle rolle er vigtige at tage højde for, når koordinationen af ikke-kirurgisk og kirurgisk behandling evalueres.

Introduction

Development of knee osteoarthritis – the knee osteoarthritis continuum

Knee osteoarthritis (OA) is a chronic disease characterized by degeneration of knee joint cartilage resulting in contact between the femur and the tibia or the patella bones leading to knee pain, knee joint stiffness and limitation in physical function (1,2). With growing age all people are affected by a natural degeneration of knee joint cartilage with varying levels of associated symptoms though not everyone experience symptoms (3,4). The process of knee joint cartilage degeneration is slow and begins years before the manifestation of knee OA symptoms (3,4). Events in early- and midlife can accelerate the cartilage degeneration (2,5–10). Participation in sports increases the risk of a severe knee joint injury such as anterior cruciate ligament or meniscus tears (2,11,12). As an example, damage to the menisci compromise their ability to shock-absorb and their ability to provide joint congruence and stability, which can lead to a to 30-50% decrease in contact pressure areas – ultimately accelerating the development of knee OA (13). Injuries to the menisci or the anterior cruciate ligament increase the risk of knee OA 4-6 fold consequently leading to an increased risk of knee joint pain later in life (2,5,6,8). Also, during adult life physically demanding labor (heavy lifting, kneeling etc.) can accelerate the degeneration of knee joint cartilage (7,9,10,14). Further, knee OA progression is associated with non-modifiable factors such as higher age, genetic predisposition and sex; and modifiable factors such as increased body weight and low levels of physical exercise (15). The process of knee joint cartilage degeneration beginning in early life to being eligible for knee replacement (KR) is known as the knee OA-continuum (Figure 1).

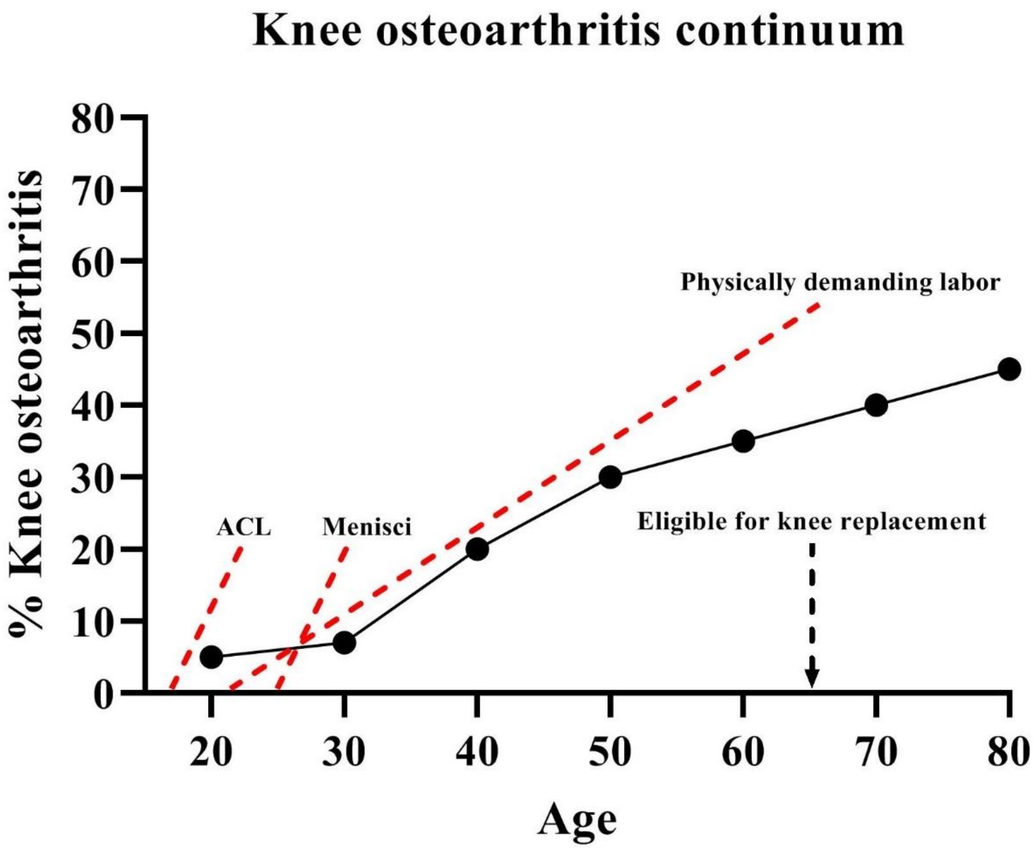

Figure 1. The knee osteoarthritis continuum. On the x-axis age in years is displayed. On the y-axis the relative development of knee osteoarthritis is displayed. The black solid line represents the theoretical development of knee osteoarthritis. The red dotted lines represent events during life which can accelerate knee joint cartilage degeneration and the development of knee osteoarthritis. ACL = Anterior cruciate ligament.

Prevalence and incidence of knee OA and knee replacement

The prevalence of knee OA has increased substantially in the past two decades and this increase in prevalence is expected to continue (16). Annually ~60.000 people in Denmark consult their general practitioner due to symptoms of knee OA and in the US ~14 million people suffer from symptomatic knee OA (17,18). In Denmark, the incidence of patients undergoing knee replacement (KR) increased from ~2.500 in 2000 to ~8.600 in 2009 and in the US an increase of 673% from the ~450.000 KR procedures performed in 2005 is expected by 2030 (18,19). This high and increasing number of patients receiving KR is a large challenge for the health care system with potential societal consequences that patients, clinicians and policy makers need to prepare for (20).

Severity of knee OA

The cardinal symptom in patients with knee OA is knee pain (1,21) while the diagnosis of knee OA is based on several factors including; the patient's medical history (i.a. knee pain, quality of life, limitations in daily living), physical examination (i.a. active and passive range of motion, palpation) and x-rays (22,23). Knee OA is roughly categorized as mild-to-moderate or severe and the main difference between the two categories is the level of symptomatology (e.g. knee pain levels) (24). Patients with severe knee OA are more likely to be deemed eligible for KR and undergo surgery (25–27). Most patients referred to KR present with severe radiographic knee OA (i.e. clear joint space narrowing, osteophytes, sclerosis and joint deformity) as this is believed to be a good indication as to whether KR will be an effective treatment (28). The level of radiographic knee OA is assessed from x-rays and commonly graded according to the Kellgren-Lawrence scale (KL) (29). However, there is often a poor relationship between the KL grade and patient-reported knee pain intensity (30,31). As an example, 30-40% of patients with severe radiographic knee OA (KL grade 3 and 4) report no knee pain (32,33).

Organization of knee OA treatment in the Danish health care system

The organization of care and care pathways in a health care system is key for successful treatment. Hence, well organized care helps both patients and clinicians to plan individualized treatment with a higher success rate (34).

In the Danish health care system non-surgical and surgical treatment is organized in different sectors. Non-surgical treatment is organized in the municipalities (primary sector) while surgical treatment is organized at the hospitals (secondary sector). This sectionalized organization poses several challenges and requires intersectoral collaboration to optimize coordination of treatment. Currently, however, there is no coordination of non-surgical and surgical treatment for patients eligible for KR, which leave patients and clinicians without a clear care pathway. Further, this makes it difficult for clinicians to comply with guideline recommendation (see paragraph below). Presently, this means that when an orthopedic surgeon refers a patient eligible for KR to exercise therapy there is no organized care pathway in which the patients' need for surgical treatment is re-assessed after exercise therapy. If the patient wishes a re-assessment by an orthopedic surgeon, the patient must be re-referred by his or her general practitioner.

Guideline recommendations – Non-surgical and surgical treatment of knee osteoarthritis

National and international guidelines recommend non-surgical treatment (e.g. pain medication, weight loss, exercise therapy, patient education) for patients with mild-to-moderate knee OA as these treatments are found effective in reducing knee OA symptoms (18,35–37). For this thesis, *exercise therapy* is defined according to the Medline Medical Subject Heading (MeSH-term) (38). For patients with severe knee OA the final treatment is KR (18,35). Before surgical procedures are undertaken, guidelines recommend that non-surgical treatment options are tried out in patients with severe knee OA (18,35,37). In line with these recommendations, exercise therapy has been found to provide clinically relevant improvements in knee OA symptoms in patients eligible for KR (39,40). Despite guideline recommendations recent findings suggest that exercise therapy is underutilized in patients with knee OA consulting an orthopedic surgeon (41).

Knee-extensor muscle strength and knee osteoarthritis

Decreased knee-extensor muscle strength is associated with increased risk of developing knee OA (5,42), increased risk of OA related knee pain and increased risk of a decline in physical function (43). Therefore, the lower knee-extensor muscle strength a patient with knee OA has the worse symptoms the patient is likely to experience. The knee-extensor muscles act as shock absorbers for the knee joint, which make sufficient knee-extensor muscle strength important in patients with knee OA (44). Correspondingly, patients eligible for KR are found to have a 35% lower knee-extensor muscle strength compared to age-matched controls, which is associated with limitations in activities of daily living (45,46). Further, acutely following surgery an additional 60-80% of the pre-operative knee-extensor muscle strength is lost, possibly resulting in prolonged rehabilitation (47–49).

Dose-response

As stated above, decreased knee-extensor muscle strength is a challenge in patients with severe knee OA. But it is a factor that can be improved with exercise therapy (50–53). Exercise programs for patients with knee OA focusing on knee-extensor strength are found to be more effective in reducing pain and disability compared to programs focusing on more general lower extremity strength (54). For dose-response and exercise, a larger exercise dosage is expected to be associated with a larger increase in muscle strength (55–57). Preferably, an exercise and associated dosage is described by the following parameters: load magnitude, number of exercises, weeks, sets and repetitions, rest, fractional and temporal distribution of the contraction modes, volitional muscle failure, range of motion and positioning (58). For patients with severe knee OA it is unclear which is the most effective knee-extensor exercise dosage (59–61).

Pre-habilitation and Enhanced Recovery After Surgery (ERAS)

Enhanced Recovery After Surgery (ERAS) is defined as a multi-professional and -disciplinary approach to improve care for patients scheduled for surgery (62–64). ERAS protocols consist of multiple care elements (e.g. multimodal analgesia, mobilization on the day of surgery, postoperative nutritional care) that all support recovery following the physical stress induced by surgery and is also referred to as “Fast Track Surgery” (62). In older patients scheduled for total hip or knee replacement, those who are treated using ERAS protocols are reported to be discharged only three days following surgery (65). A treatment modality within ERAS, is the concept of pre-habilitation (64,66).

Pre-habilitation stems from the “better in – better out” paradigm and is referred to as an intervention aiming to improve the physical capacity of a patient prior to a stressful event (e.g. surgery), so that the patient can withstand the negative consequences of the event better and avoid decrease in perioperative functional status (67–69). Consequently, improvements after surgery is based on the existence of improvements before surgey (61). Pre-habilitation is a commonly used intervention prior to surgery in various medical specialties, e.g. lung cancer- and abdominal aortic aneurysm surgery (70,71). In relation to the KR population, a systematic review did not find effect of pre-habilitation (i.a. aerobic and strength exercise) on pain and function before total knee arthroplasty (61). For the purpose of this thesis, pre-habilitation is referred to as exercise therapy prior to KR surgery. In theory, pre-habilitation in patients eligible for KR increases knee muscle strength and functional capacity prior to surgery leading to less decline following surgery and potentially a faster and easier re-habilitation (Figure 2) (67,69,72).

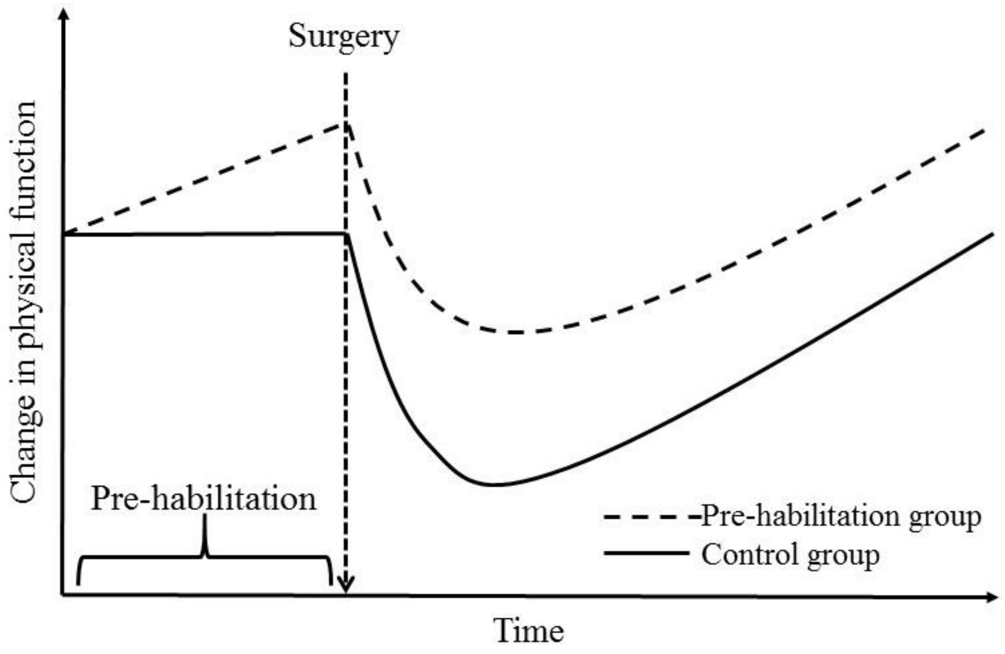

Figure 2. Theoretical model of pre-habilitation. Modified from Carli and and Zavorsky (69) and Topp et al. (72).

Home-based exercise and adherence

Exercise therapy is effective in improving physical performance and muscle strength in healthy populations as well as in patients with various conditions (55,73,74). Exercise therapy is often conducted in outpatient group-based sessions, which is also the case for the treatment of patients with knee OA (75–77). However, outpatient group-based exercise sessions may not be the best solution for all types of patients. For example, it can be impractical for those who are still active on the labor market or those who have long distances to exercise facilities. A substitution or a supplement to outpatient exercise sessions is home-based exercise after exercise instruction. In rehabilitation following KR recent findings suggest no difference between the two types of rehabilitation (78). Home-based exercise encourages patients to take a more active part in the treatment of their condition and to learn how to self-manage their treatment (37,79,80). Another advantage of teaching patients to self-manage their treatment is that the patients will have tools for self-managing future symptoms (81). However, home-based exercise places high demands on the patients' independence and skills in performing the exercises correctly (82). A challenge related to home-based exercise is adherence, which is reported to be poor (83–86). Adherence is critical to the effectiveness of exercise therapy as it must be maintained for the effect to sustain (87).

Shared decision-making

The term "shared decision-making" describes the collaboration between a health care professional and a patient when making an informed clinical decision – a decision that enhances the chance of treatment success in a planned care pathway based on individual patient preferences (88–90). This patient-centered approach to clinical decision-making is becoming more frequent as an increasing number of patients desire an active role in the treatment of their condition (91). An increased focus on patient involvement facilitates a change from a paternalistic model, where the physician informs the patient of the treatment and care pathway, to a more patient-centered approach (90). This change in the patient-physician relationship has led to the shared decision-making model (90). Information about outcomes, risks, costs and benefits for each treatment option is important when guiding patients to the optimal individual treatment option (91). Health care professionals play a very important role in providing this information (90,91). Shared decision-making can facilitate better communication between health care professionals and patients leading to improved outcomes for patients (92). With shared decision-making, treatment decisions become better aligned with patient expectations, which can improve patient satisfaction and lead to increased compliance (92). In line with this, patients who are informed about the best available evidence related to their condition and associated treatment options are more likely to take active part in their treatment (93). This patient-centered approach allows for healthcare professionals to be more responsive to patient preferences. Thereby a shared responsibility for clinical decision-making can be developed and this can improve treatment outcomes and patient satisfaction (94).

Stakeholder involvement

When researchers investigate new initiatives in established organizations, the inclusion of stakeholder input is crucial for successful identification of facilitators and barriers to adjust the intervention and to facilitate implementation (95,96). Three overarching study designs exist to assess effectiveness and implementation. The choice of design depends on the level of available clinical- and implementation strategy- evidence (97). These study designs are referred to as hybrid I-III and are characterized as follows: 1) Hybrid I – primary aim: determine effectiveness of a clinical intervention; secondary aim: better understand context for implementation; 2) Hybrid II – Coprimary aim: determine effectiveness of a clinical intervention, coprimary aim: determine feasibility and potential utility of an implementation intervention and 3) Hybrid III – Primary aim:

determine utility of an implementation intervention; secondary aim: assess clinical outcomes associated with implementation trial (97).

The purpose of including stakeholders and identifying context specific facilitators and barriers is to avoid resources being used on initiatives that prove to be non-feasible and not worth implementing in a given setting (96,98). When investigating new treatment initiatives in the health care system, the key stakeholders are the clinicians and the patients. To know whether the initiative under study can be integrated with existing procedures and if so, how this done most optimally, it is important to involve clinicians who work on a daily basis in the organization (98,99).

This PhD thesis on the knee OA continuum

The majority of research investigating the effect of exercise therapy on patients with knee OA is conducted in patients with mild-to-moderate knee OA where exercise therapy is found to be moderately effective (36,79). This leaves the unanswered question of whether exercise therapy is also effective in patients with severe knee OA, who are eligible for KR. Thus, this thesis focuses on patients with severe knee OA, who are eligible for KR, and the coordination of non-surgical and surgical treatment for this patient population. Optimization of treatment for patients with knee OA is part of the strategy for the clinical academic group *Research OsteoArthritis Denmark – Prevention and treatment through the lifespan of patients (ROAD)*. The thesis specifically matches the purpose of work package 7 – PERIEX (peri-operative exercise to enhance recovery following total hip and knee replacements: is it of any clinical value?). This work package is part of the collective research strategy for the clinical academic group *ROAD* (100).

Summary

In summary, there are important gaps in the literature related to the care and treatment of patients eligible for KR. Exercise therapy is an effective treatment modality in patients with mild-to-moderate knee OA, especially exercise therapy focusing on knee-extensor muscle strength. However, there is a lack of literature on the dose-response effect of different knee-extensor exercise dosages in patients eligible for KR. Further, on an organizational level, no coordination of surgical and non-surgical treatment for patients eligible for KR currently exists, leaving patients with suboptimal treatment options. Finally, when investigating new initiatives in the health care system, involvement of stakeholders such as orthopedic surgeons and physiotherapists is key to identify potential challenges.

Aims and Hypotheses

The aims of the PhD thesis were to investigate a coordinated care pathway of non-surgical and surgical treatment, and if a dose-response relationship exists between pre-operative knee-extensor exercise and outcomes before and after surgery in patients eligible for knee replacement. The thesis is part of the PREHAB-KR project. Four studies constitute the thesis each using a different methodology to investigate the aims. Firstly, a systematic review (study I), which serves as a "state-of-the-art" basis for the thesis, and secondly the parent study; a clinical dose-response trial (study II+III). Finally, the clinical trial and an embedded qualitative study (study IV) investigates stakeholder perspectives on a coordinated care pathway of non-surgical and surgical treatment in patients eligible for KR.

Study I (systematic review)

Purpose

To evaluate the dose-response relationship between knee-extensor muscle strength exercise dosage in pre-habilitation and the effect on knee-extensor muscle strength (primary outcome), performance-based function and patient-reported outcomes (secondary outcomes) prior to and following total knee arthroplasty in patients with severe knee OA.

Hypothesis

A positive relationship exists between knee-extensor muscle strength exercise dosage and increase in knee-extensor strength, performance-based function and patient-reported outcomes prior to total knee arthroplasty and less decline following total knee arthroplasty.

Study II (QUADX-1 trial protocol paper) + III (QUADX-1 trial results dissemination)

Purpose

To investigate the efficacy of three different exercise dosages (two, four and six exercise sessions per week) of pre-operative, homebased, knee-extensor strength exercise on knee-extensor strength before and shortly after surgery in patients eligible for KR due to severe knee OA.

Hypothesis

A dosage of four knee-extensor strength exercise sessions per week will elicit a greater strength increase pre-operatively compared to two or six sessions per week.

Study IV (qualitative study)

Purpose

To identify perceived facilitators and barriers - among orthopedic surgeons and physiotherapists – towards coordinated non-surgical and surgical treatment of patients with severe knee OA using pre-operative home-based exercise therapy with *one* exercise.

Hypothesis

No hypothesis was provided in this study due to the explorative nature of the design.

Methods

Selection and inclusion of trials for the systematic review (study I) was based on a rigorous literature search and clear in- and exclusion criteria. Inclusion of patients for the clinical trial (study II+III) took place at the Orthopedic Department at Copenhagen University Hospital Hvidovre between November 2016 and January 2019. Patients were consecutively included and randomized based on a computer-generated list. Participants for the qualitative study (study IV) were recruited based on the premise that they were involved in the clinical trial (study II+III). An overview of the study designs is presented in Table 1. The following methods sections are based partly on text from Paper II and Manuscript I and IV to ensure methodologically consistency and transparency. Great care has been taken to avoid self-plagiarism - as defined by the Graduate School of Health and Medical Sciences, University of Copenhagen (https://healthsciences.ku.dk/phd/thesis-and-defence/screening-for-duplicate-text/) - by correct referencing of own work.

Study aim	Design	Investigators	Included patients/participants	Outcomes
Study I (systematic review). To evaluate the dose response relationship between knee-extensor muscle strength exercise dosage in pre-habilitation and effect on knee-extensor muscle strength, performance-based function and patient-reported outcomes prior to and following total knee arhtroplasty in patients with end-stage knee OA.	Systematic review and meta-regression analysis of randomized controlled trials.	Five physiotherapists (RSH, TB, KT, MSR, CJ) One orthopedic surgeon (AT) One statistician (TK)	• 4550 articles after systematic literature search and duplicate removal. • 4510 excluded after title/abstract screening. • 40 full-text articles assessed. • 12 articles included (616 patients).	Primary: • Knee-extensor strength Secondary: • Patient-reported outcomes • Performance-based function
Study II+III (QUADX-1 trial) (Study II = protocol article, study III = results dissemination). To investigate the efficacy of three different exercise dosages (two, four and six exercise sessions per week) of pre-operative, homebased, knee-extensor strength exercise on knee-extensor strength before and shortly after surgery in patients eligible for KR due to severe knee OA.	Randomized dose-response trial (protocol + results).	Six physiotherapists (RSH, TB, KT, MSR, LH, BG) Two orthopedic surgeons (AT, HH). One statistician (TK)	• 140 patients with written informed consent and baseline assessment. • 23 drop out/missing data prior to primary end-points. • 117 with complete data sets at the primary end-point.	Primary: • Isometric knee-extensor strength Secondary: • Oxford Knee Score • Knee Osteoarthritis Outcome Score • Current knee pain (NRS 0-10) • Average knee pain during past week (NRS 0-10) • Need for surgey (Yes, Don't know, No) • Stair climbing test • Six-minute walk test • Exercise adherence
Study IV (qualitative study). To identify perceived facilitators and barriers - among orthopedic surgeons and physiotherapists – towards coordinated non-surgical and surgical treatment of patients with severe knee osteoarthritis using pre-operative home-based exercise therapy with *one* exercise.	Qualitative study of interviews (focus group and single interviews).	Three physiotherapists (RSH, TB, MSR) One orthopedic surgeon (AT) One nurse (JK)	• Six physiotherapists. • Four orthopedic surgeons.	Themes emerging from thematic analysis, including barriers and facilitators.

Table 1. Study design overview for study I-IV. RSH: Rasmus Skov Husted, TB: Thomas Bandholm, KT: Kristian Thorborg, MSR: Michael Skovdal Rathleff, CJ: Carsten Juhl, AT: Anders Troelsen, TK: Thomas Kallemose, LH: Line Holst, BG: Birk Grønfeldt, HH: Henrik Husted, JK: Jeanette Kirk.

Study I (systematic review)

The following method section is based on text from Manuscript I. The systematic review was pre-registered on PROSPERO (CRD42018076308) 4/1-2018. The protocol followed the PRISMA-P guidelines (101) and is reported according to the PRISMA guideline (102) (Manuscript I).

Inclusion criteria

Included trials had to be designed as randomized controlled trials investigating pre-habilitation in patients scheduled for total knee arthroplasty (TKA) due to knee OA. The pre-habilitation intervention had to comprise at least one resistance training (Medline MeSH definition) (103) exercise targeting the knee-extensor muscles, e.g. sitting knee-extension or leg-press. The trials had to have an outcome assessment before surgery, that is, an assessment of the effect of the exercise intervention before surgery and this pre-operative outcome assessment had to comprise an assessment of the knee-extensor muscle strength. The comparator could either be described as care as usual, no intervention, patient education, placebo control, a lower exercise dosage than the intervention group or exercise not defined as resistance training. Trials with follow-up assessments after TKA were also included to evaluate whether effects before surgery improved outcomes after TKA (Manuscript I).

Literature search and study selection

A systematic literature search was performed 27th of August 2019 in the following databases: Medline, CENTRAL, Embase and CINAHL using MeSH terms and text words related to knee OA and exercise therapy – the full search string for Medline is available online (104). This search strategy was applied to all databases. Reference lists of included trials were scanned for potentially relevant references to ensure data saturation. No limits regarding language or date were applied. To limit the search to randomized controlled trials, the *Cochrane Highly Sensitive Search Strategy for identifying randomized trials* was applied (105). All identified titles and abstracts were screened for eligibility by two independent reviewers (RSH and TB). All trials judged eligible by one reviewer were obtained in full text and assessed in detail according to the eligibility criteria. In case of disagreement, a third reviewer (MSR) was consulted (Manuscript I).

Extracted data items and data collection process

The following data items were extracted for description and analyses from the included trials.

- *Trial-related data:* Year of publication, authors, design, registration (prospectively or not), follow-up time-points and number of patients allocated to intervention and control group.
- *Patient-related data:* Sex, age, body mass index (BMI), baseline level of knee pain and radiographic severity of knee OA.
- *Intervention-related data:* Type and number of knee-extensor exercises, length of intervention (weeks), number of exercise sessions per week, number of sets per exercise session, number of repetitions per set, intensity of the exercise (repetition maximum (RM/% of 1 RM)) and a description of other exercises in the intervention. For extraction of exercise related data, the Consensus on Exercise Reporting Template (CERT) (106) and the mechanobiological exercise descriptors suggested by Toigo and Boutellier (58) were used as the template.
- *Control group data:* A brief description of the intervention (if any).
- *Outcome-related data:* Primary outcome; knee-extensor strength (e.g. isometric or isokinetic measurements). Secondary outcomes; knee pain, patient-reported function (e.g. activities of daily living), knee-related performance-based function (e.g. six-minute walk test and stair climb test) and adverse events.

To increase validity of the data extraction, double data extraction was applied with RSH and MSR independently extracting data from the included trials. The online software covidence.org was used and the extracted data was cross-checked for differences (Manuscript I).

Assessment of risk of bias in the individual trials

The original Cochrane *Risk of Bias Tool* (107) was used to assess risk of bias in the included trials. The domains *sequence generation*, *allocation concealment*, *blinding of participants, personnel and outcome assessor*, *incomplete outcome data*, *selective outcome reporting* and *other sources of bias* were evaluated as to whether there was *low*, *unclear* or *high risk of bias*. The risk of bias evaluation was completed independently by RSH and TB. In case of disagreement, MSR was used as an arbitrator (Manuscript I).

Study II+III (QUADX-1 trial)

Disclaimer

No results from the post-operative assessments will be presented in the thesis as assessment of the final three patients was scheduled for after the thesis submission deadline. For the same reason, the QUADX-1 trial is not unblinded for the thesis. Therefore, for the remainder of the thesis, the three exercise dosages will be referred to as group A, B and C (not knowing which exercise dosage these cover) and not the dosage prescribed. The following method section is based on text from Paper II (108).

Trial design and patients

The QUADX-1 trial is an assessor blinded, three-arm parallel-group randomized dose-response trial with three intervention groups and no control group (108). Between November 2016 and January 2019, patients eligible for KR at the Orthopedic Department at Copenhagen University Hospital, Hvidovre were invited to participate. The trial was pre-registered at clinicaltrials.gov on October 10, 2016 (NCT02931058). A approvals from the Ethics Committee of the Capital Region of Denmark (H-16025136) and the Danish Data Protection Agency (2012-58-0004) were obtained before the first patient was enrolled. The trial is reported according to the CONSORT checklist (109).

Patients fulfilling the following inclusion criteria were included by consecutive sampling: eligible for KR due to knee OA, radiographically verified knee OA with Kellgren-Lawrence classification ≥ 2, average knee pain in the last week ≥ 3 (Numeric Rating Scale (NRS)), eligible for home-based knee-extensor exercise, age ≥ 45 years, resident in one of three municipalities (Copenhagen, Hvidovre or Brøndby) involved in the trial and able to speak and understand Danish. Patients were excluded if exercise was contra-indicated, they had a neurological disorder, they had a diagnosed systemic decease (American Society of Anesthesiologists' physical status classification score (ASA) ≥ 4), they had a terminal illness, they had severe bone deformity demanding usage of non-standard implants or if they had a weekly alcohol consumption above the national recommendations (110) (Paper II) (108).

Interventions

Following baseline assessment and randomization, the patients were referred to a physiotherapist at their local municipality rehabilitation setting and instructed on how to perform *one* knee-extensor exercise. The knee-extensor exercise was performed sitting on a chair with an elastic exercise band wrapped around the ankle for resistance. The exercise band was fixated behind a door with an anchor. The patients were handed personal exercise bands for exercising at home and a brochure with instruction notes. The knee-extensor exercise is illustrated in Figure 3 and an online video (111). The rational for using *one* exercise was that it is pragmatic, time-saving and thus can facilitate adherence and a mastery of the exercise (84,112,113). Further, it is unknown if several exercises that stresses the same muscle tissue adds muscular strength benefits (57), while *one* exercise stresses the knee joint minimally.

Figure 3. The home-based, knee-extensor strength exercise.

The patients were instructed to exercise at home for twelve weeks. After four and eight weeks, the patients re-visited the physiotherapist at the municipality setting to have an exercise quality and knee symptom check-up. The exercise check-up included a re-assessment of the exercise technique (fractional and temporal distribution of the contraction modes, range of motion and positioning), ensuring exercise resistance corresponded to 12 repetition maximum (RM) (adjusting length and type of exercise band), exercise-related questions from the patients and knee pain flare questions.

The patients were randomized to one of three weekly exercise dosages: two, four or six sessions per week for twelve weeks. In all groups, each exercise comprised the single knee-extensor strength exercise. At all sessions, the exercise was performed in three sets with 12 repetitions at a load corresponding to 12 repetion maximum (RM) in each set (Table 2). The exercise was personalized with individual absolute resistance in the exercise band corresponding to a relative load of 12 RM. The exercise should continue until volitional muscular failure. If volitional muscular failure occurred before 12 repetitions or more than 12 repetitions could be performed, the resistance in the exercise band was adjusted to a resistance corresponding to 12 RM. The patients were instructed to perform only one exercise session per day, thus not to combine several sessions on the same day. For detailed information on the exercise please see the protocol paper (108) (Paper II) (108).

Dosage groups	**Sessions/week**					
Group 2 - 2 sessions/week	3*12 RM			3*12 RM		
Group 4 - 4 sessions/week	3*12 RM	3*12 RM		3*12 RM	3*12 RM	
Group 6 - 6 sessions/week	3*12 RM	3*12 RM	3*12 RM	3*12 RM	3*12 RM	3*12 RM

Table 2. Knee-extensor exercise dosages investigated. RM = repetition maximum.

Outcome assessments and outcomes

Outcomes were assessed blinded at four end-points; at baseline (t_0), after twelve weeks of home-based exercise/before surgery (t_1), at hospital discharge (1-8 days after surgery) (t_2) and three months after surgery (t_3). End-points t_2 and t_3 were provided that surgery was performed (*NB, as mentioned in the disclaimer, the two end-points after surgery (t_2+t_3) are omitted for the thesis*). The primary end-point was after the exercise period (t_1) and the secondary end-points were just before hospital discharge (t_2) and three months after surgery (t_3) (Figure 7 of Paper II) (Paper II) (108).

Primary outcome

The primary outcome was change in isometric knee-extensor strength from baseline to after the exercise period (t_0-t_1). The knee-extensor strength assessments were performed using a computerized strength chair (Good Strength Chair, Metitur Oy, Jyvaskyla, Finland). This is a valid (0.78–0.92) and reliable (inter-trial 0.98–1.00, inter-evaluator 0.92–0.99) measure of change in knee-extensor strength in the TKA population (114). Five measurements of maximal isometric knee-extensor contraction at 60° knee flexion separated by 60-s pauses were completed. The patients were instructed to extend their knee as forcefully as possible with a gradual increase in force over a 5-s period while receiving strong standardized verbal encouragement. The knee-extensor strength is expressed as the maximal voluntary torque per kilogram body mass (Nm/kg). The highest obtained value was used for the analysis (Paper II) (108).

Secondary outcomes

The secondary outcomes were change in performance-based function: six-minute walk test (6MWT) and stair climb test (SCT), self-reported disability: Knee Osteoarthritis Outcome Score (KOOS) and Oxford Knee Score (OKS), current knee pain and average knee pain during the last week (0-10 NRS), "need for surgery" and objectively measured exercise adherence. Also, adverse events were registered.

The "need for surgery" outcome was an assessment of the patients' self-perceived need for surgery. After the exercise period, at outcome assessment t_1, the patients were asked by the outcome assessor: *"Based on your knee symptoms in the last week, would you say that you need knee surgery?"* Three answers were possible: 1) *"Yes, I believe I need surgery"*, 2) "*I do not know"* or 3) *"No, I do not believe I need surgery"*.

Exercise adherence was objectively quantified using a sensor (BandCizer technology) attached to the exercise band. The sensor stores data on date, time, number of sets, number of repetitions and time-under-tension (TUT). The sensor technology has been reported to be valid and reliable for measuring date, time of day, number of sets, repetitions and TUT during commonly used strength exercises for musculoskeletal conditions (115–117). In the present trial, patients were defined as adherent if >75% of the prescribed exercise sessions were completed. For details on other outcomes, please see Paper II (108).

Following outcome assessments, data was entered in the browser-based research database Research Electronic Data Capture (REDCap 7.1.1) by trial personnel. To ensure data validity, blinded double-data entry was applied (Paper II) (108).

Sample size

For the planned three-group One-way ANOVA a sample size of 126 (42 per group) patients was required to obtain a power of 80%. A normal mean difference test with a two-sided significance level of 5% was used for the a priori sample size calculation with a minimal clinically important difference of 0.15 Nm/kg (15%) and a common standard deviation of 0.22 Nm/kg in isometric knee-extensor strength (118). To allow for a drop-out rate of 10%, 140 patients were included for the intention-to-treat (ITT) analysis (Paper II) (108).

Randomization, sequence generation, allocation concealment mechanisms and implementation

The patients were randomly assigned to one of the three exercise groups (two, four or six sessions per week) by a 1:1:1 allocation ratio. The random allocation sequence was computer-generated by a statistician who was otherwise not involved in the trial. One hundred and forty sequentially numbered, sealed, opaque envelopes were generated. When a patient had been included in the trial (signed written informed consent and completed baseline assessment), a research assistant who was independent of the trial opened the assigned envelope and informed the patient's municipality of the exercise group allocation. In this way, the outcome assessors were kept blinded to the allocation (Paper II) (108).

Blinding

All outcome assessors and data analysts were blinded to the exercise group allocation. At all the beginning of the outcome assessments, the assessors informed the patients not to mention their exercise dosage. For analysis, the data were coded so that group allocation was concealed and thereby the data assessors and analysts were blinded to the allocation. The physiotherapists and patients were not blinded to the allocation due to the nature of the intervention. The patients were blinded to the other exercise dosages and the trial hypothesis (Paper II) (108).

Study IV (qualitative study)

Design and context

The following method section is based on text from Manuscript IV. The PREHAB-KR project was designed with an interventional trial (the QUADX-1 trial (study II+III) (108)) with concurrent gathering of information for clinical implementation and applicability, also referred to as a Hybrid I design (97). This qualitative study is thus an embedded study in the QUADX-1 trial and involves analysis of interviews with physiotherapists and orthopedic surgeons involved in the

QUADX-1 trial. These two professions were interviewed as they are the main stakeholders in the health care system working with patients with severe knee OA. Interviews were chosen as data collection method since this is a recognized qualitative method for obtaining in-depth knowledge about stakeholders' feelings, experiences and attitudes (119,120) (Manuscript IV).

Study participants

We recruited four orthopedic surgeons and six physiotherapists. Eligible participants had to be involved in the QUADX-1 trial since the intervention under study was not implemented in routine clinical practice. Thus, the ten participants represent all potential participants (Manuscript IV).

Interviews (focus group and single interviews) and procedures

The original study plan was to apply focus group interviews for both groups of health professionals. Focus group methodology was chosen as this is a recognized method to facilitate a setting in which participants can express and discuss their experiences freely as well as listen to experiences of other participants (119–121). A focus group interview was completed with physiotherapists. Due to tight work schedules for the orthopedic surgeons, it proved impossible to conduct a focus group interview with this group of health professionals. As a compromise, single interviews were conducted instead – a method suitable for producing in-depth data on a specific topic or phenomenon (122). All interviews were guided by semi-structured interview guides (Appendix 2 and 3 in Manuscript I). The guiding questions were open-ended and a "funnel" approach was applied starting with broad questions followed by probing and sensitizing questions to facilitate more detailed information (119).

The interviews were conducted before the first patient was enrolled in the QUADX-1 trial to ensure that the participants had no experience with neither the trial nor the intervention before the interview. Thus, the content of the interviews only relates to the preconceptions among the orthopedic surgeons and physiotherapists and not their later experience with the trial (Manuscript IV).

Statistical and qualitative analyses

Due to the different methodological approaches in each study there is no overlap in the analytical methods used. For elaborated details pertaining to the individual studies, please see the full papers and manuscripts at the end of the thesis.

Study I (systematic review)

Meta-regression analyses

To investigate the dose-response relationship between knee-extensor exercise dosage in pre-habilitation and the effect on knee-extensor muscle strength, knee pain, patient-reported function and knee related performance before and three months after TKA, meta-regression analyses were performed. To account for as many exercise descriptors as possible, we defined knee-extensor exercise dosage as:

$$\text{Knee-extensor exercise dosage} = (knee * w * s * se * r) * \frac{i}{r}$$

Abbreviation explanation: knee = number of knee-extensor exercises, w = weeks, s = sessions per week, se = sets per session, r = repetitions per set, i = exercise intensity (estimated % 1 RM).

The meta-regression analyses were adjusted for the following co-variates to evaluate their impact: age, sex, BMI, knee pain at baseline, knee-extensor strength at baseline and whether the control group received an active (exercise therapy) or passive (e.g. information) intervention of the lower extremities (Manuscript I).

Elaboration of exercise-dosage calculation

The exercise-dosage calculation was developed in collaboration with a statistician, a physiologist and physiotherapists. In 10 of the 12 included trials, the exercise intensity was not reported according to the RM principle (123). To compensate for this missing information, we estimated the exercise intensity based on the number of repetitions using the Holten curve (124). As an example, 11 repetitions correspond to an exercise intensity of 80% of 1 RM. The *total number of repetitions* (knee*w*s*se*r) was multiplied with the *exercise intensity* divided by *repetitions per set* (i/r) to normalize the exercise dosage to the 1 RM scale/the Holten curve. The *exercise intensity* was divided by *repetitions per set* to ensure that the exercise dosage was not overestimated in trials with a high total number of prescribed repetitions with low exercise intensity compared to trials with a lower total number of prescribed repetitions with higher exercise intensity. For example, a trial with 11 repetitions per set corresponding to 80% of 1 RM would have a total exercise intensity per set of 880% (11*80) while a trial with 16 repetitions per set, corresponding to 75% of 1 RM, would have a total exercise intensity per set of 1.200% (16*75). In this scenario, the trial with low exercise intensity is given a higher total exercise dosage. By dividing the *exercise intensity* with *repetitions per set* this overestimation is normalized corresponding to the exercise intensity resulting in 80% and 75%, respectively.

Meta-analyses

To evaluate the difference in effect between the intervention and the control groups across the included trials, meta-analysis statistics were applied. As outcomes within the same construct were reported using different scales, results are presented as standardized mean differences (SMD). For example, the outcome *knee-extensor muscle strength* was reported on both isometric and isokinetic scales. All data were continuous and effect sizes are presented as SMDs with 95% confidence intervals (CI). Results of the meta-analyses are presented in forest-plots. Between-trial inconsistency was assessed with I^2 statistics, where I^2 statistics of 30-60% were defined as moderate heterogeneity. A fixed effects model was used if I^2 statistics were <30% and if statistical heterogeneity was observed (I^2 statistics >30%), the random effects model was used. To investigate potential small trials with large effect (small study bias), a funnel plot was conducted. If the funnel plot suggested small study bias, Eggers regression test and the “trim and fill” method was used to investigate this further. In case of heterogeneity, trial characteristics were analyzed in meta-regression analyses to try and explain this. All analyses were performed using using Stata statistical software version 11.0 (Manuscript I).

Study II+III (QUADX-1 trial)

Descriptive statistics were calculated with mean and ±SD for normally distributed data. Normal distribution of data was checked using q-q plots and histograms. For all outcomes, between group contrasts were compared using repeated measures of variance (One-way ANOVA). Residuals for the analyses were checked for normal distribution to ensure that the underlying assumptions of the statistical model were met. Results are presented as absolute changes (e.g. Nm/kg) firstly and secondly, as relative changes (%) from baseline. Mean scores with ±SD, between group contrasts (change scores) with 95% CI and p-values for each outcome at each time-point across all three groups are reported. As supplementary analyses, simple regression models were performed using pooled exercise adherence data across all three groups. Patients were excluded from the regression analyses if less than six exercise sessions were recorded. The dependent variables were the primary and secondary outcomes and the independent variable, exercise adherence, was quantified in two ways: 1) as total "time-under-tension" and 2) as number of completed exercise sessions per patient. All analyses followed the ITT principle and missing data were imputed using multiple imputation with imputating from linear regression models. All analyses were performed using SAS Enterprise Guide version 7.1. Multiple imputation was done using the *proc mi* procedure with the *fcs reg* option in SAS (Paper II) (108).

Study IV (qualitative study)

Thematic analysis

Following verbatim transcription, the interviews were merged into one text representing the unit of analysis. Before beginning the analysis, the interviews were read through several times by RSH to obtain a sense of the whole. The interviews were analyzed and grouped into themes and associated sub-themes by RSH and JK using inductive thematic analysis (125). The analytical process involved 1) dividing the text into meaning units, 2) condensing the meaning units, 3) abstracting and coding the condensed meaning units, 4) sorting codes based on similarities and differences, 5) sorting codes into sub-categories and categories and finally 6) analyzing the latent content (underlying meaning) of the categories and formulating these into themes.

After the initial analysis, the tentative categories were discussed and re-analyzed by the research team in an iterative process of reflection and discussion (126). Categories were then revised to strengthen the validity of the results. The final themes were agreed upon by the whole research team (Manuscript IV).

Results

A summary of the main results from study I-IV is listed below. For further details on study I and IV, please see the Manuscripts I and IV. The pre-operative results from the QUADX-1 trial (study II+III) are presented below. The following results sections are based on text from Manuscript I and IV.

Study I (systematic review)

Study selection

The following result section is based on text from Manuscript I. The literature search yielded 9514 hits. After removal of duplicates, 4550 hits were screened for title and abstract. Following title and abstract screening, 4510 articles were excluded and 40 articles were read in full text. Of these, 28 were excluded and 12 included for data extraction and analysis (Figure 4). Characteristics of the included trials and risk of bias within trials is available in Table 1 and Figure 2 of Manuscript I (Manuscript I).

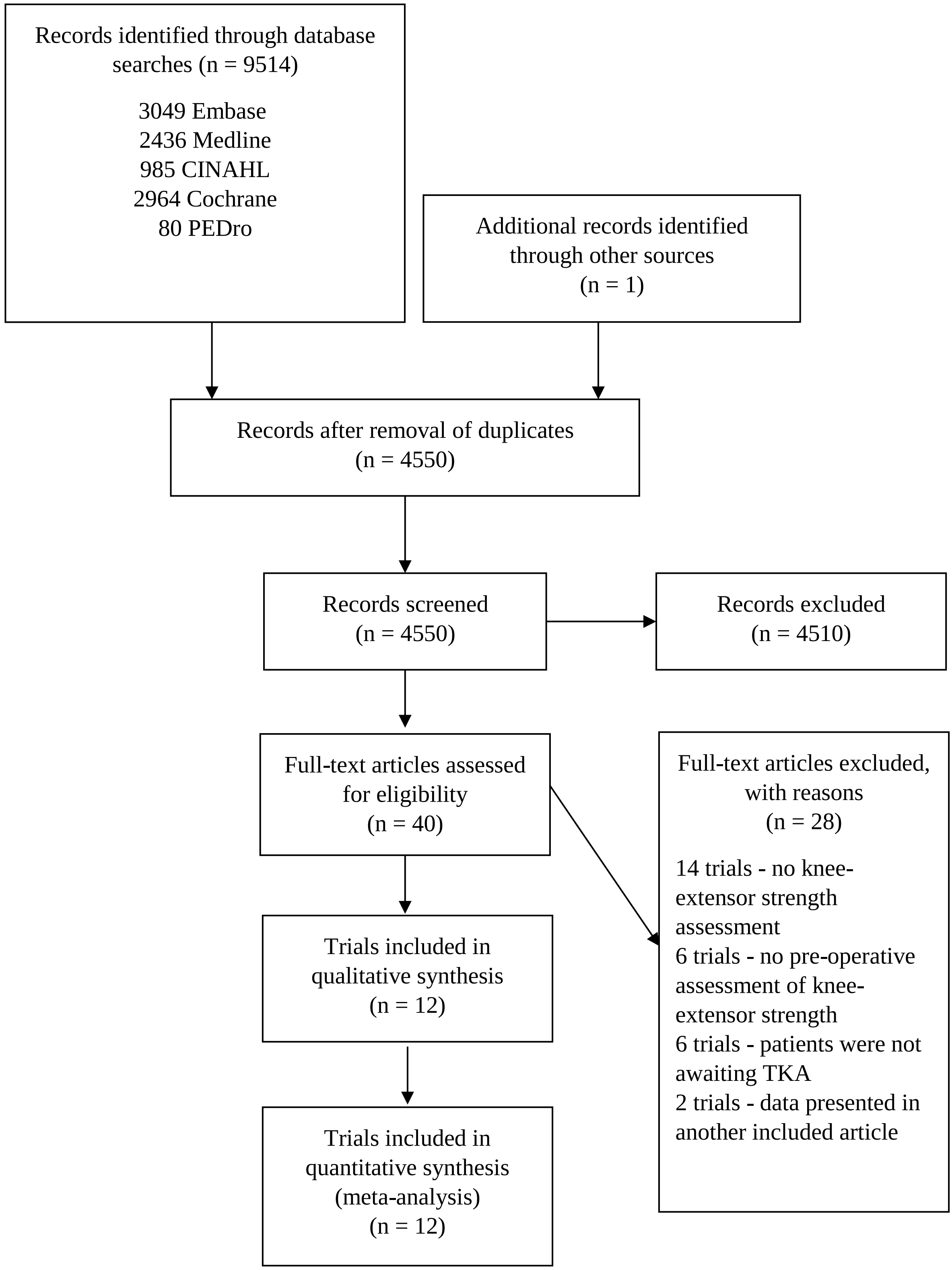

Figure 4. Flowchart of included trials, presented in accordance with the PRISMA 2009 guidelines (102). Twelve trials were included in the final qualitative synthesis and quantitative analysis. RCT = randomized controlled trial, OA = osteoarthritis, TKA = total knee arthroplasty.

Pre-operative dose-response relationship

Twelve trials reported the effect of pre-habilitation including knee-extensor strength exercise on pre-operative knee-extensor strength (51–53,127–135). Meta-regression analysis showed no relationship between pre-habilitation knee-extensor exercise dosage and knee-extensor strength prior to TKA (slope 0.0005 [95% CI -0.007 to 0.008]) (Figure 5). An inverse relationship was found between pre-habilitation knee-extensor exercise dosage and Timed “Up & Go” prior to TKA (slope -0.019 [95% CI -0.032 to -0.006]). No relationship was found between knee-extensor dosage and the outcomes knee pain, function, stair climbing test, short distance walk test and six-minute walk test prior to TKA (Table 3) (Manuscript I).

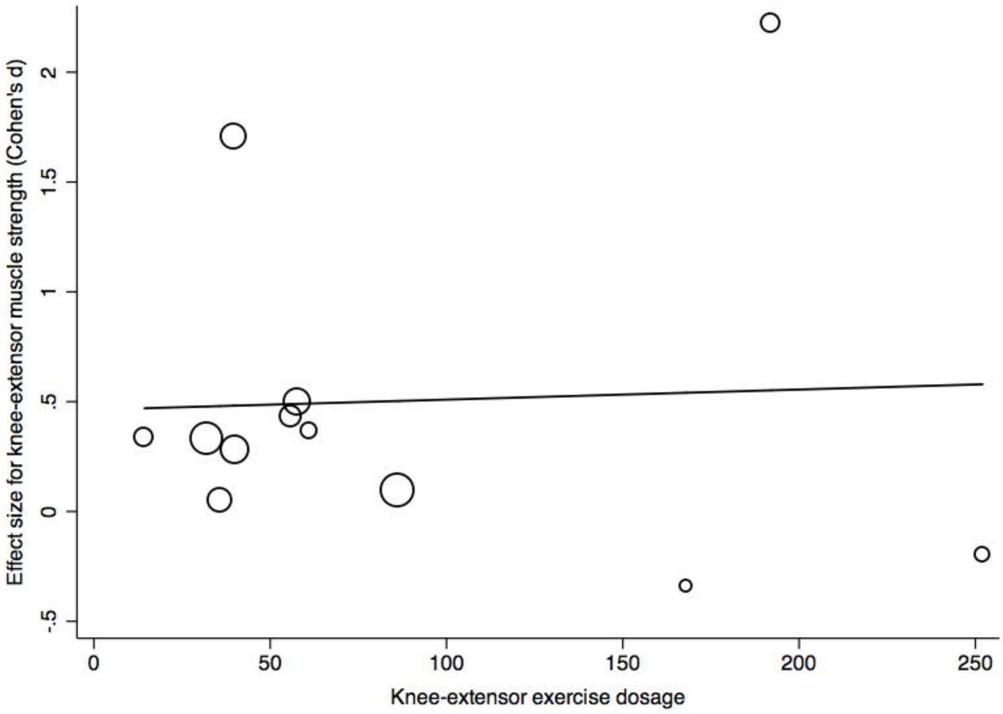

Figure 5. Unadjusted meta-regression analysis on the relationship of knee-extensor exercise dosage and pre-operative muscle strength. On the x-axis the independent variable is displayed, pre-habilitation knee-extensor exercise dosage: (number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. On the y-axis the effect size (SMD) of the dependent variable, pre-operative knee-extensor strength, is displayed. The solid black line shows the slope of the relationship between the knee-extensor exercise dosage and the effect-size on muscle strength. The individual trials are shown by circles and the weight of the individual trials is illustrated by the size of the circles (i.e. larger circles indicating larger weight).

Post-operative dose-response relationship

Nine trials reported on the effect of pre-habilitation including knee-extensor strength exercise on three months post-operative knee-extensor strength (51,52,127,129,131–135). Meta-regression analysis showed no relationship between pre-habilitation knee-extensor exercise dosage and knee-extensor strength three months following TKA (slope 0.0014 [95% CI -0.006 to 0.009]). No relationship was found between knee-extensor dosage and the outcomes knee pain, function, stair climbing test, short distance walk test and six-minute walk test three months following TKA (Table 3).

Neither pre- nor post-operative results were altered when adjusting for the co-variates: age, BMI, knee-extensor strength at baseline and whether the control group received an active or passive intervention of the lower extremities. No adjustment was made for knee pain at baseline due to lack of observations (Manuscript I).

Independent variable	**Dependent variable**	**Slope**	**95% CI**
	Prior to TKA		
Pre-habilitation knee-extensor exercise dosage	Knee-extensor strength	0.0005	-0.007 to 0.008
	Knee pain	-0.012	-0.028 to 0.004
	Patient-reported function	0.016	-0.005 to 0.038
	Stair climbing test	-0.005	-0.063 to 0.052
	Timed “Up & Go”	-0.019	-0.032 to -0.006
	Short distance walk test	0.012	-0.007 to 0.031
	Six-minute walk test	-0.006	-0.101 to 0.088
	Three months following TKA		
	Knee-extensor strength	0.0014	0.006 to 0.009
	Knee pain	-0.003	-0.12 to 0.006
	Patient-reported function	0.004	-0.006 to 0.016
	Stair climbing test	-0.0.13	-0.365 to 0.338
	Timed “Up & Go”	-0.012	-0.050 to 0.024
	Short distance walk test	0.012	-0.007 to 0.031
	Six-minute walk test	N.A.	N.A.

Table 3. Pre-habilitation knee-extensor exercise dosage = (number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. N.A. = too few observations for analysis.

Pre-operative effects of pre-habilitation

The meta-analysis showed a moderate effect favoring pre-habilitation for an increase in knee-extensor strength prior to TKA (SMD 0.50 [95% CI 0.12 to 0.88]), with substantial heterogeneity (I^2 = 78.5%) (Figure 6). For the secondary outcomes, pre-habilitation did not significantly improve knee pain, patient-reported function, stair climbing test, Timed "Up & Go", short distance walking (15-25 m) or six-minute walk test prior to TKA (Figure 7). Large heterogeneity (I^2 >30%) was present in all meta-analyses and a random effects model was performed (Manuscript I).

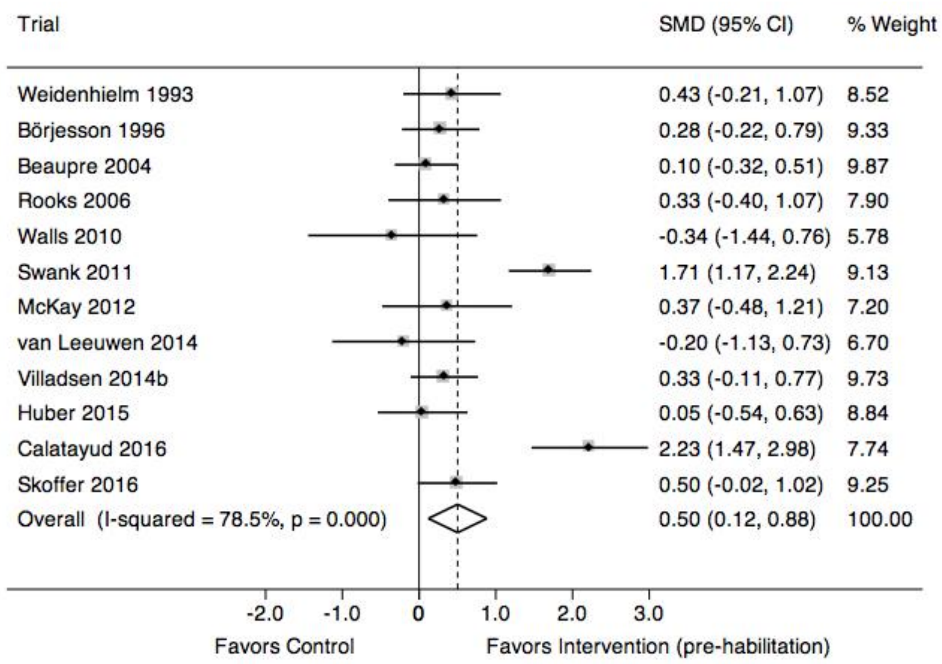

Figure 6. Forest plot of the effect of pre-habilitation including knee-extensor exercise on pre-operative knee-extensor muscle strength. SMD = standardized mean difference. Individual trials and total effects are shown with 95% confidence intervals ((SMD (95% CI)). Weights are from a random effect analysis.

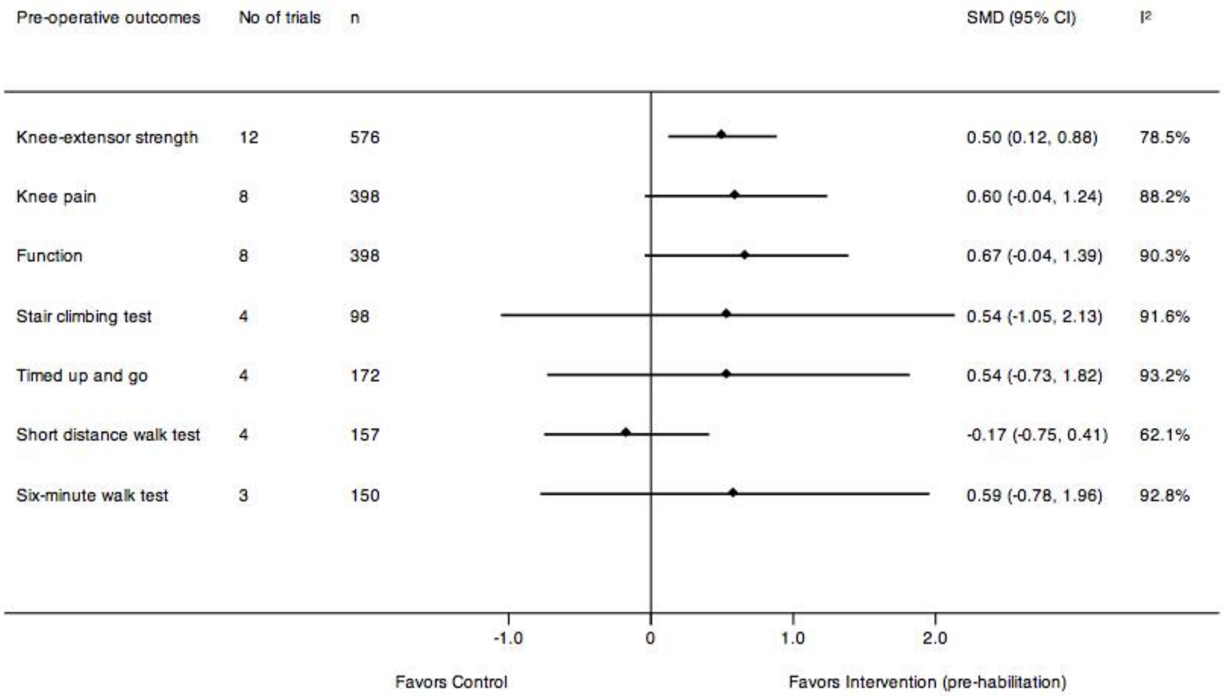

Figure 7. Forest plot of pooled effect sizes for all pre-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

Post-operative effects of pre-habilitation

No effect of pre-habilitation on knee-extensor strength three months following TKA was found (SMD -0.01 [95% CI -0.45 to 0.43]) (Figure 8), with substantial heterogeneity (I^2 = 77.3%). No effect of pre-habilitation was seen in any post-operative outcomes (Figure 9) (Manuscript I).

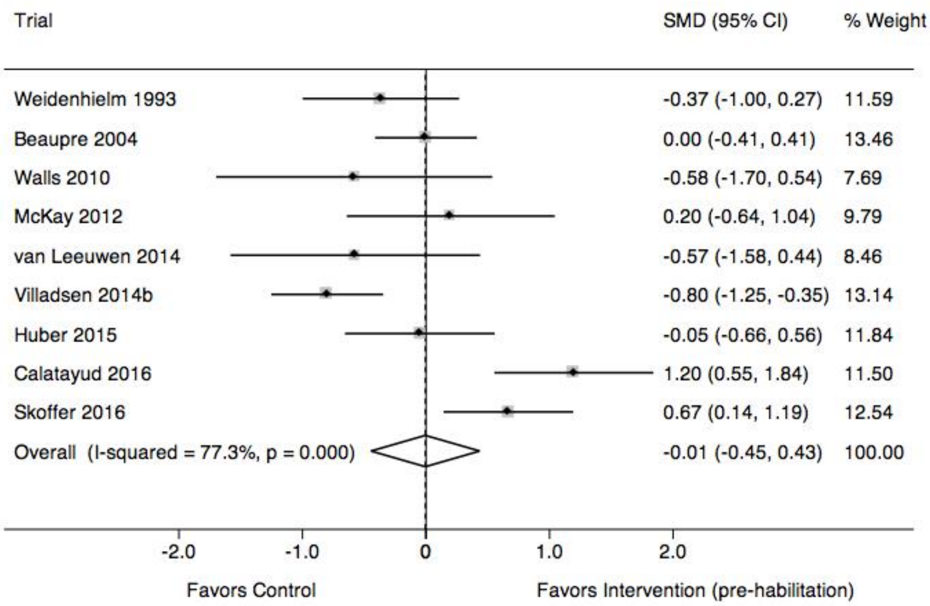

Figure 8. Forest plot of the effect of pre-habilitation including knee-extensor exercise on three months post-operative knee-extensor muscle strength. SMD = standardized mean difference. Individual trials and total effects are shown with 95% confidence intervals ((SMD (95% CI)). Weights are from a random effect analysis.

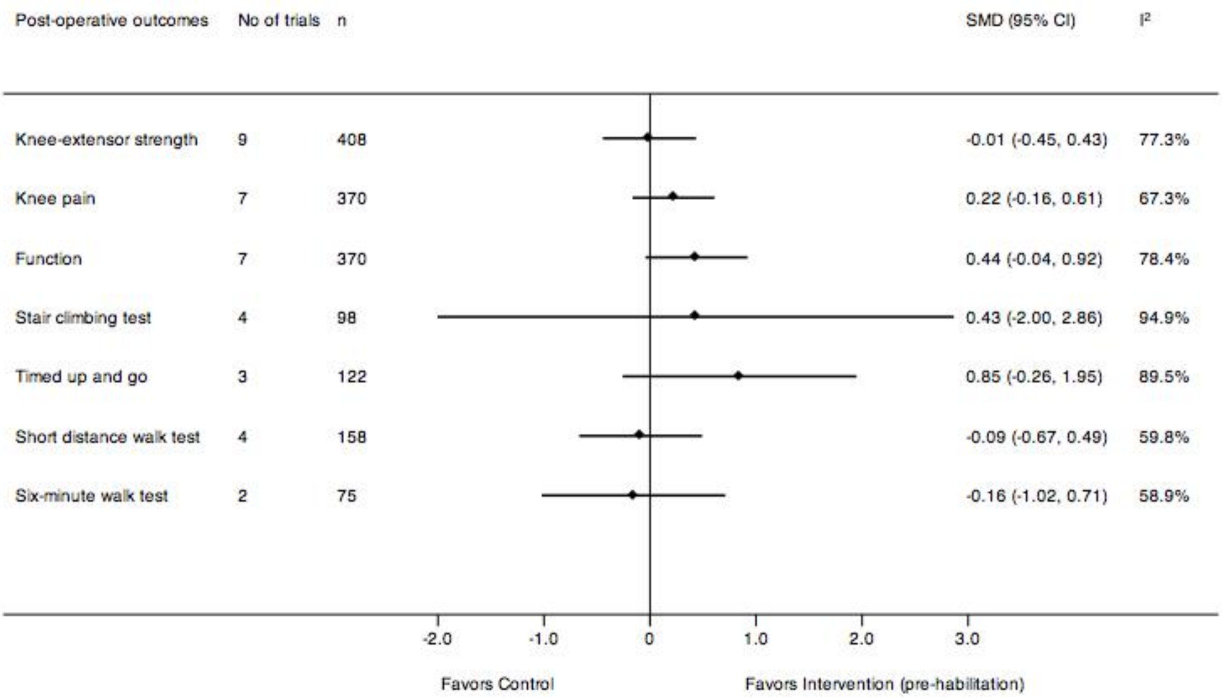

Figure 9. Forest plot of pooled effect sizes for all three months post-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

Risk of small study bias and exploring heterogeneity

No indication of clear asymmetry was identified in the funnel plot and Eggers regression test showed no small-study effect. Between-study variance was seen in the meta-analysis on pre-operative knee-extensor strength (Tau^2 = 0.3394). Between-study variance was reduced when meta-regression analysis was adjusted for sex expressed as percentage of women in individual trials (Tau^2 = 0.126) (slope 0.0540 [95% CI 0.016 – 0.0915]). This implies that with a 10% increase in women in the study, the SMD for knee-extensor muscle strength would increase by 0.5 (Manuscript I).

Study II+III (QUADX-1 trial)

Between November 2016 and January 2019, 898 patients potentially eligible for KR were assessed for eligibility. One-hundred and forty patients were included and randomized to an exercise dosage of '2 session/week', '4 session/week' or '6 sessions/week' (Figure 10, Flow chart). For the remainder of the thesis, these exercise dosages will be referred to as group A, B and C not knowing which exercise dosage they cover. Assessments at the primary end-point (after 12 weeks of exercise) (t_1) was completed for 117 patients with 39 in each of the three groups. Reasons for drop-out and missing data for each group before the primary end-point are provided in the flow chart (Figure 10). For the intention-to-treat analysis, 140 patients were included. Baseline characteristics are provided in Table 4 for the whole sample and for each group separately. The baseline characteristics are comparable between the three groups (no statistical hypothesis testing was undertaken as suggested by the CONSORT group (109)).

Baseline characteristics (t0)

Characteristics	All patients n = 140	Group A n = 47	Group B n = 46	Group C n = 47
Gender (f/m)	74/63	27/17	25/21	22/25
Age (years)	66.7 (9.9)	66.8 (10.0)	65.8 (10.0)	67.5 (9.7)
Weight (kg)	91.9 (19.9)	94.2 (21.8)	89.8 (20.3)	92.1 (17.0)
Height (cm)	169.2 (8.3)	170.1 (7.7)	169.1 (9.9)	168.7 (7.0)
Municipality (Cph/Hvi/Brø)	74/44/22	23/16/8	29/12/5	22/16/9
Kellgren and Lawrence score (2/3/4)	20/61/54	9/19/15	6/22/18	5/20/21
Current knee pain (NRS 0-10)	2.2 (2.2)	2.1 (2.2)	2.4 (2.1)	2.1 (2.4)
Avg. knee pain last week (NRS 0-10)	5.8 (1.6)	5.8 (1.6)	5.8 (1.4)	5.7 (1.6)
Knee-extensor strength (Nm/kg)	1.27 (0.53)	1.22 (0.5)	1.28 (0.5)	1.31 (0.6)
KOOS Symptoms (0-100)	55.0 (18.8)	53.4 (16.7)	52.9 (19.6)	58.9 (19.4)
KOOS Pain (0-100)	49.7 (16.4)	48.2 (16.7)	49.6 (15.5)	51.7 (16.5)
KOOS ADL (0-100)	55.3 (17.5)	51.7 (17.5)	56.3 (17.3)	57.7 (17.0)
KOOS Sport (0-100)	21.0 (20.8)	16.8 (16.7)	21.3 (20.1)	24.5 (23.6)
KOOS QoL (0-100)	32.7 (16.3)	31.2 (16.1)	31.1 (15.9)	35.4 (16.3)
OKS (0-48)	24.8 (7.6)	23.2 (8.0)	24.9 (7.0)	26.2 (7.3)
6MWT (m)	402.3 (105.3)	387.7 (112.2)	402.1 (102.8)	416.5 (94.1)
SCT up (secs)	9.4 (5.1)	10.3 (5.4)	9.0 (4.6)	8.7 (5.1)
SCT down (secs)	10.4 (6.7)	11.9 (7.9)	10.4 (6.4)	8.9 (5.3)

Table 4. Values are presented as means ± SD. Cph = Copenhagen, Hvi = Hvidovre, Brø = Brøndby, KOOS = Knee Osteoarthritis Outcome Score, OKS = Oxford Knee Score, 6MWT = six-minute walk test, SCT = Stair climb test

CONSORT 2010 Flow Diagram

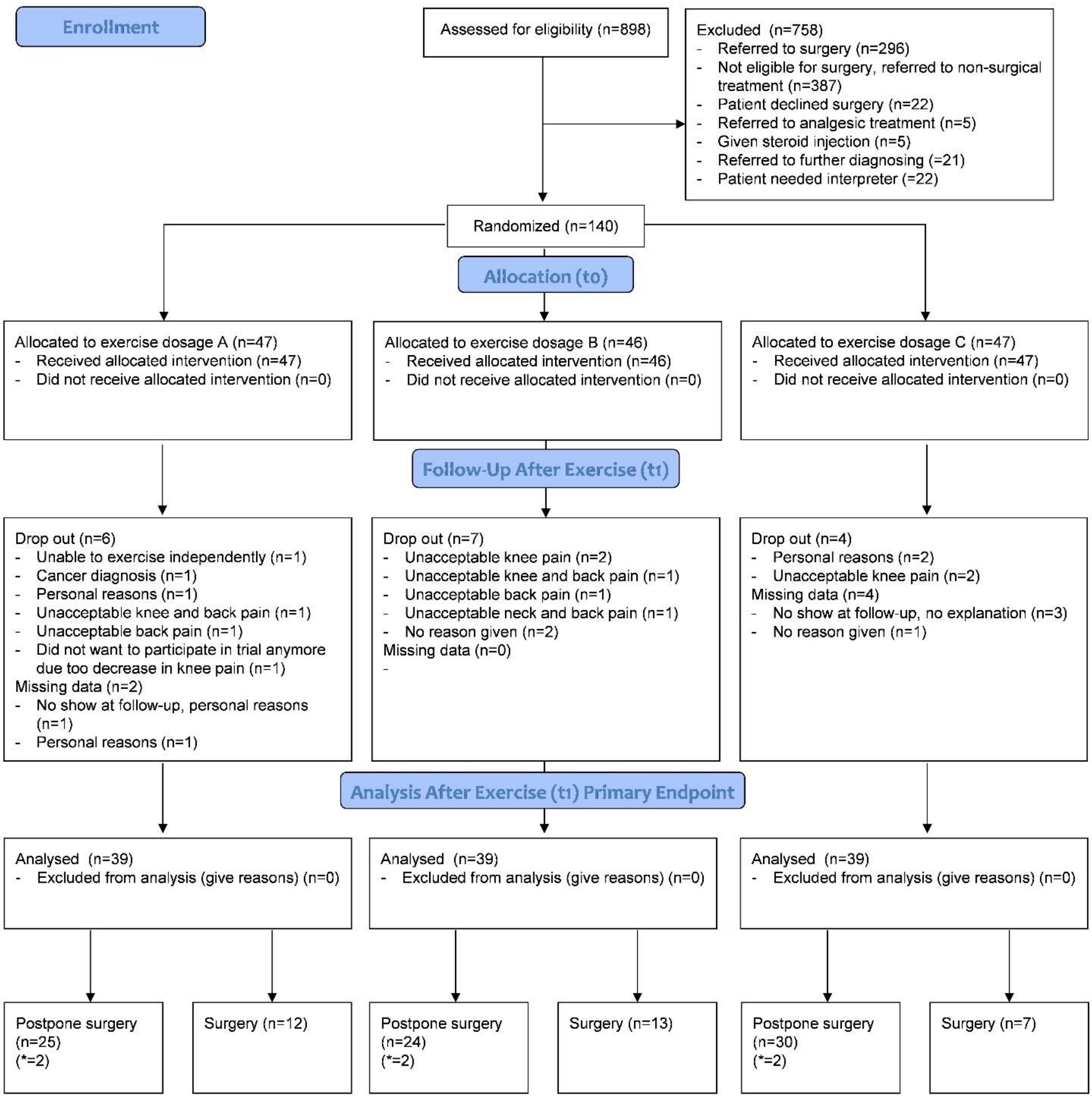

Figure 10. Flow chart of each pre-operative stage of the trial according to CONSORT guidelines (109). *6 patients wanted surgery but had competing co-morbidities disqualifying them as candidates for surgery (Appendix 1).

Outcome measurement scores

The outcome scores for the primary and secondary outcomes at the primary end-point (t_1) are presented in Table 5. Outcome scores for the secondary end-points (t_2 and t_3) are not provided in the thesis, as outcome assessments of the final three patients were scheduled for after thesis submission deadline.

Primary outcome – Knee-extensor strength (Nm/kg): The ITT analysis showed no difference in change from baseline to after 12 weeks of exercise (primary end-point) in *isometric knee-extensor muscle strength* between the three groups (Group B vs. A 0.04 Nm/kg [95% CI -0.13 to 0.20], p=0.6685), group C vs. A (0.009 Nm/kg [95% CI -0.15 to 0.17], p=0.9131) and group C vs. B (-0.03 Nm/kg [95% CI -0.18 to 0.13], p=0.7253) (Figure 11). Within group changes from baseline to after 12 weeks of exercise showed an increase for the whole sample and all three groups separately, though not significant for group A (Whole sample [0.13 Nm/kg (95% CI 0.07 to 0.19], p=<0.0001), group A (0.11 Nm/kg [95% -0.007 to 0.23], p=0.0646), group B (0.15 Nm/kg [95% CI 0.04 to 0.25], p=0.0078) and group C (0.12 Nm/kg [95% 0.02 to 0.22], p=0.0213)).

Secondary outcomes: The ITT analysis showed a significant difference in change from baseline to after 12 weeks of exercise between group C and B for *Oxford Knee Score* (4.2 OKS points [95% CI 0.6 to 7.8], p=0.0216) (Figure 12) and *average knee pain last week* (NRS 0-10) (-1.1 NRS points [95% -2.2 to -0.1], p=0.0303). No between group differences were observed for any other group comparisons or secondary outcomes at the primary end-point. Within group changes showed a positive change for the whole sample, and all three groups separately, for all secondary outcomes at the primary end-point. Larger changes were observed in group C compared to group A and B, and in group A compared to group B. For the outcome "*need for surgery*"; 37 patients answered "*Yes, I believe I need surgery*", 25 "*I don't know*" and 55 "*No, I do not believe I need surgery*". For answers across the three groups, see Table 5.

Mean change in all outcomes from baseline and following 12 weeks of home-based exercise (t0-t1) (intention-to-treat analysis, n = 140). One-way ANOVA on imputed data.

	Mean change (95% CI) from baseline (effect = time)			Mean change (95% CI) from baseline (effect = time*group)			
	Mean change within groups (95% CI)	P	% change within groups		Mean change between groups (95% CI)	P	% change between groups
Knee-extensor strength (Nm/kg)							
All patients	0.13 (0.07 to 0.19)	<0.0001	10.2%				
Group A	0.11 (-0.007 to 0.23)	0.0646	9.0%	Group B vs. A	0.04 (-0.13 to 0.20)	0.6685	2.7%
Group B	0.15 (0.04 to 0.25)	0.0078	11.7%	Group C vs. A	0.009 (-0.15 to 0.17)	0.9131	0.1%
Group C	0.12 (0.02 to 0.22)	0.0213	9.2%	Group C vs. B	-0.03 (-0.18 to 0.13)	0.7253	-2.6%
KOOS Symptoms							
All patients	9.1 (5.6 to 12.6)	<0.0001	16.5%				
Group A	8.0 (2.6 to 13.4)	0.0036	17.0%	Group B vs. A	-1.7 (-10.3 to 6.9)	0.6988	-4.8%
Group B	6.5 (0.5 to 12.5)	0.0327	12.3%	Group C vs. A	4.9 (-3.6 to 13.4)	0.2573	4.9%
Group C	12.9 (6.2 to 19.6)	0.0002	21.9%	Group C vs. B	6.4 (-2.2 to 14.9)	0.1444	9.6%
KOOS Pain							
All patients	9.9 (6.7 to 13.2)	<0.0001	19.9%				
Group A	9.7 (4.7 to 14.8)	0.0002	20.1%	Group B vs. A	-2.8 (-10.7 to 5.2)	0.4925	-6.4%
Group B	6.8 (1.4 to 12.2)	0.0140	13.7%	Group C vs. A	3.8 (-3.9 to 11.5)	0.3313	6.4%
Group C	13.7 (7.5 to 19.8)	<0.0001	26.5%	Group C vs. B	6.9 (-1.3 to 15.0)	0.0984	12.8%
KOOS ADL							
All patients	9.2 (5.9 to 12.4)	<0.0001	16.6%				
Group A	9.5 (3.9 to 14.9)	0.0007	18.4%	Group B vs. A	-2.5 (-10.4 to 5.5)	0.5416	-6.1%
Group B	6.9 (1.3 to 12.7)	0.0158	12.3%	Group C vs. A	2.1 (-5.8 to 10.0)	0.6033	1.7%
Group C	11.6 (6.0 to 17.2)	<0.0001	20.1%	Group C vs. B	4.6 (-3.5 to 12.7)	0.2593	7.8%
KOOS Sport							
All patients	8.4 (4.3 to 12.6)	<0.0001	40.0%				
Group A	6.9 (0.5 to 13.5)	0.0360	41.1%	Group B vs. A	0.3 (-10.1 to 10.7)	0.9558	-5.9%
Group B	7.5 (1.3 to 13.6)	0.0168	35.2%	Group C vs. A	3.8 (-6.3 to 13.9)	0.4531	2.6%
Group C	10.7 (2.0 to 19.5)	0.0159	43.7%	Group C vs. B	3.3 (-7.0 to 13.6)	0.5304	8.5%
KOOS QoL							
All patients	8.2 (4.6 to 11.8)	<0.0001	25.1%				
Group A	7.3 (1.6 to 12.9)	0.0125	23.4%	Group B vs. A	-1.8 (-10.1 to 7.7)	0.7926	-4.1%
Group B	6.0 (-0.6 to 12.7)	0.0760	19.3%	Group C vs. A	4.2 (-4.7 to 12.9)	0.3510	9.4%
Group C	11.6 (4.9 to 18.2)	0.0006	32.8%	Group C vs. B	5.6 (-3.5 to 14.6)	0.2265	13.5%

OKS							
All patients	4.5 (3.0 to 5.9)	<0.0001	18.1%				
Group A	4.9 (2.6 to 7.1)	<0.0001	21.1%	Group B vs. A	-2.6 (-6.2 to 0.9)	0.1388	-11.9%
Group B	2.3 (-0.3 to 4.8)	0.0805	9.2%	Group C vs. A	1.6 (-1.9 to 5.1)	0.3666	3.3%
Group C	6.4 (3.8 to 9.0)	<0.0001	24.4%	Group C vs. B	4.2 (0.6 to 7.8)	0.0216	15.2%
Current pain							
All patients	-0.3 (-0.8 to 0.1)	0.1685	-13.6%				
Group A	-0.1 (-0.9 to 0.6)	0.7093	-4.8%	Group B vs. A	-0.3 (-1.5 to 0.8)	0.5632	-16.1%
Group B	-0.5 (-1.3 to 0.3)	0.2648	-20.8%	Group C vs. A	-0.2 (-1.3 to 0.9)	0.7007	-14.3%
Group C	-0.4 (-1.2 to 0.4)	0.3276	-19.0%	Group C vs. B	0.1 (-1.0 to 1.2)	0.8877	1.8%
Pain last week							
All patients	-1.2 (-1.6 to -0.8)	<0.0001	-20.7%				
Group A	-1.1 (-1.8 to -0.4)	0.0017	-19.0%	Group B vs. A	0.4 (-0.6 to 1.5)	0.3988	6.9%
Group B	-0.7 (-1.4 to 0.04)	0.0622	-12.1%	Group C vs. A	-0.7 (-1.7 to 0.3)	0.1571	-12.6%
Group C	-1.8 (-2.6 to -1.1)	<0.0001	31.6%	Group C vs. B	-1.1 (-2.2 to -0.1)	0.0303	-19.5%
6MWT							
All patients	19.2 (3.0 to 35.4)	0.0202	4.8%				
Group A	10.9 (-16.6 to 38.6)	0.4352	2.8%	Group B vs. A	1.7 (-39.2 to 42.6)	0.9337	0.5%
Group B	13.5 (-15.4 to 42.5)	0.3590	3.4%	Group C vs. A	24.1 (-16.2 to 64.4)	0.2379	5.3%
Group C	33.7 (3.5 to 63.8)	0.0288	8.1%	Group C vs. B	20.1 (-22.0 to 62.3)	0.3451	4.7%
SCT up							
All patients	-0.9 (-1.6 to -0.2)	0.0106	-9.6%				
Group A	-1.4 (-2.6 to -0.1)	0.0316	13.6%	Group B vs. A	1.3 (-0.4 to 3.1)	0.1401	13.0%
Group B	-0.05 (-1.1 to 0.9)	0.9297	-0.6%	Group C vs. A	0.03 (-1.8 to 1.8)	0.9764	-2.5%
Group C	-1.4 (-2.8 to 0.1)	0.0655	-16.1%	Group C vs. B	-1.3 (-3.1 to 0.5)	0.1518	15.5%
SCT down							
All patients	-1.4 (-2.3 to -0.5)	0.0018	-13.5%				
Group A	-2.1 (-3.9 to -0.2)	0.0287	-17.6%	Group B vs. A	1.3 (-1.4 to 2.9)	0.2630	10.0%
Group B	-0.8 (-2.1 to 0.5)	0.2040	-7.7%	Group C vs. A	0.7 (-1.4 to 2.9)	0.5010	1.9%
Group C	-1.4 (-2.8 to 0.1)	0.0607	-15.7%	Group C vs. B	-0.5 (-2.7 to 1.6)	0.6249	-8.0%
"Need for surgery"*							
	'Yes'		'I don't know'			'No'	
All patients (n=117)	37 (31.6%)		25 (21.4%)			55 (47.0%)	
Group A (n=39)	13 (33.3%)		7 (18.0%)			19 (48.7%)	
Group B (n=39)	15 (38.5%)		11 (28.2%)			13 (33.3%)	
Group C (n=39)	9 (23.1%)		7 (18.0%)			23 (58.9%)	

Table 5. Data presented with mean change value and corresponding 95% confidence interval. Knee-extensor strength reported as Nm/kg (positive change = improvement); Knee Osteoarthritis Outcome Score (KOOS) subscale reported on 0-100 scale (positive change = improvement); Oxford Knee Score (OKS) reported on 0-48 scale (positive change = improvement); Pain scores reported on Numeric Raring Scales (NRS 0-10) (negative change = improvement); Six-minute walk test (6MWT) reported in meters (positive change = improvement); Star climb test (SCT) reported in seconds (negative change = improvement).*Patients' self-perceived need for surgery was assessed with the outcome

“need for surgery”. Following the exercise period the patients were asked by the outcome assessor: *“Based on your knee symptoms in the last week, would you say that you need knee surgery?”* Three answers were possible: 1) *“Yes, I believe I need surgery”*, 2) “*I do not know”* or 3) *“No, I do not believe I need surgery”*.

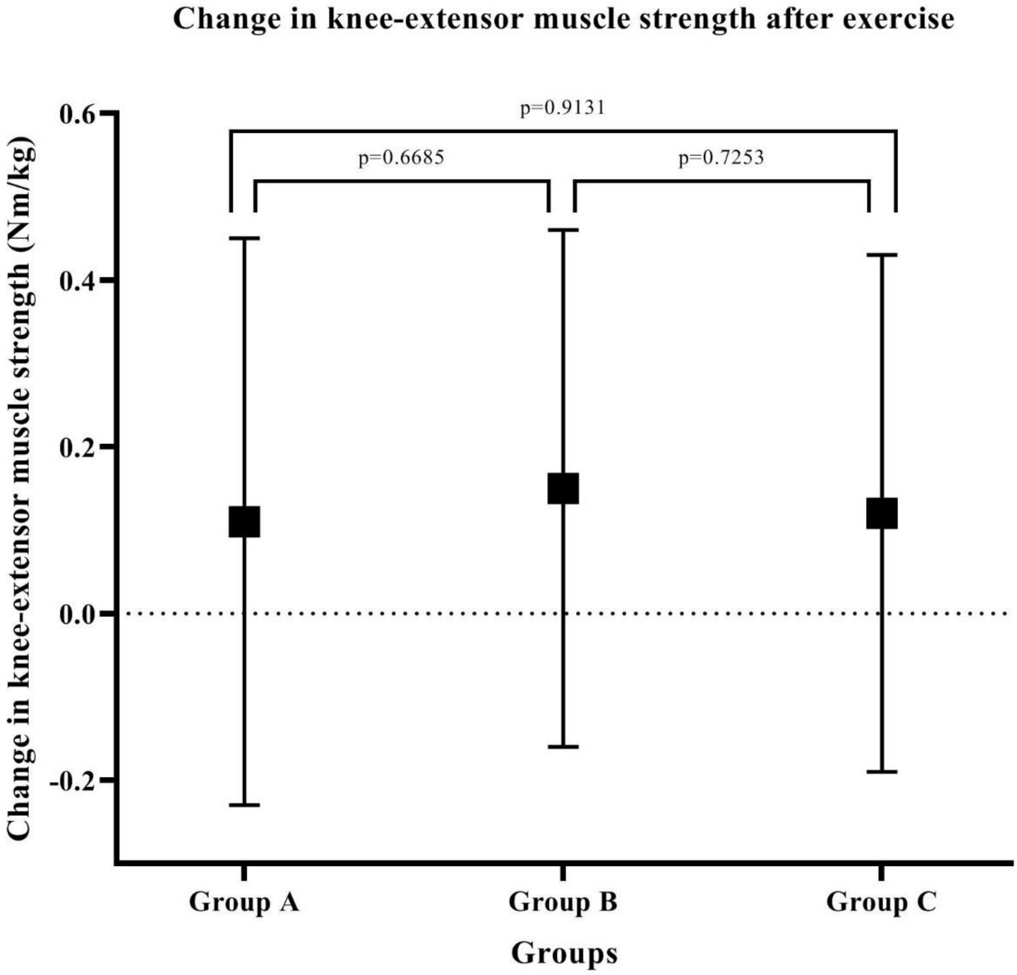

Figure 11. Change in knee-extensor muscle strength (Nm/kg) after twelve weeks of home-based knee-extensor exercise across the three groups.

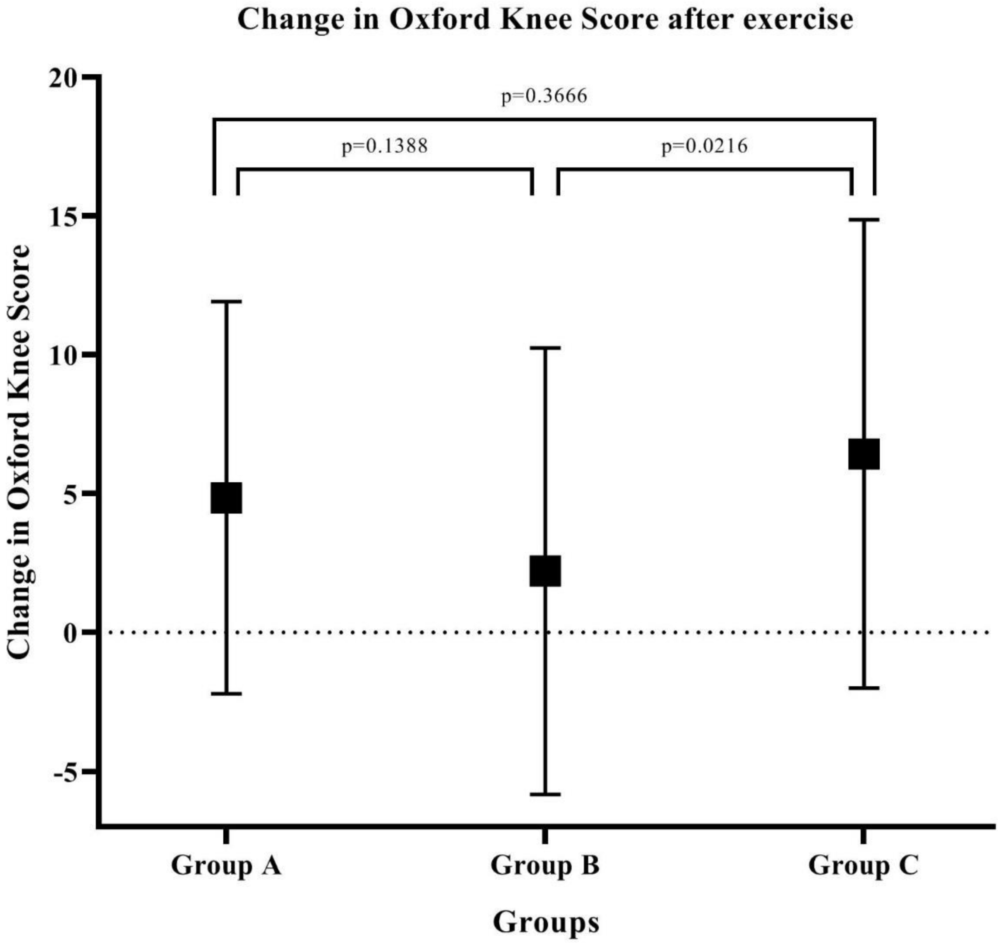

Figure 12. Change in Oxford Knee Score after twelve weeks of home-based knee-extensor exercise across the three groups.

Treatment decision after exercise

Of the 117 patients with follow-up assessments (Figure 10), 79 (67.5%) postponed surgery, 32 (27.4%) underwent KR and 6 (5.1%) wanted surgery but this was contra-indicated due to co-morbidities (Appendix 1) (Table 6). Post hoc analysis showed no significant difference between the number of patients postponing surgery and the number of patients undergoing KR between the three groups (X^2 test, p=0.2564).

Treatment decision after home-based exercise

	All patients n = 117	Group A n = 39	Group B n = 39	Group C n = 39
Postponed surgery, n (%)	79 (67.5%)	25 (64.1%)	24 (61.6%)	30 (76.9%)
Surgery, n (%)	32 (27.4%)	12 (30.8%)	13 (33.3%)	7 (18.0%)
Wanted surgery but surgery was contra-indicated, n (%)	6 (5.1%)	2 (5.1%)	2 (5.1%)	2 (5.1%)

Table 6. Distribution of treatment decision across the whole sample and the three groups, number and percentage.

Adverse events

In total, nine adverse events were registered between baseline and assessment after exercise, with two events in group A and C and five events in group B. The main adverse event related to the exercise intervention was increased knee pain (n=6). All six patients dropped out of the trial before the primary end-point due to knee pain.

Simple regression models

As a supplementary analysis, simple regression models were performed analyzing the association between objectively assessed exercise adherence and change in pre-operative outcomes. The three groups were pooled into one sample for the regression analyses. Data from 95 patients was available for the regression analyses. Of the 45 patients without available data 23 did not complete the 12 weeks of exercise (dropped-out and missing data), 8 had less than six recorded exercise session and 14 had technical problems or lost the Bandcizer sensor. Exercise adherence was quantified as total time-under-tension (TUT) and total number of sessions. No association was observed between the level of exercise adherence and pre-operative changes for any outcomes, except for a weak inverse association between total number of sessions and change in the *six-minute walk test* (Slope -0.7323 [95% -1.819 to -0.1826] (Table 7). The association implies that for every completed exercise session, the change in *six-minute walk test* will be 0.7 meters less.

Independent variable	Dependent variable - Change scores from baseline to primary end-point	Slope	95% CI
Exercise adherence quantified as total TUT			
	Knee-extensor muscle strength (Nm/kg)	-0.000006	-0.00001 to 0.000003
	KOOS Symptoms	0.000007	-0.0007 to 0.0008
	KOOS Pain	-0.00009	-0.0007 to 0.0006
	KOOS ADL	0.00004	-0.0006 to 0.0007
	KOOS Sport	-0.00004	-0.0009 to 0.0008
	KOOS QoL	-0.0004	-0.0011 to 0.0004
	OKS	-0.0002	-0.0005 to 0.0002
	Current pain (0-10 NRS)	-0.00004	-0.0001 to 0.00005
	Avg. pain last week (0-10 NRS)	0.00002	-0.00008 to 0.0001
	SMWT (meters)	-0.0022	-0.0044 to 0.00006
	SCT up (seconds)	0.00001	-0.00009 to 0.0001
	SCT down (seconds)	-0.00007	-0.0002 to 0.00008
Exercise adherence quantified as total number of sessions			
	Knee-extensor muscle strength (Nm/kg)	-0.0015	-0.0037 to 0.0008
	KOOS Symptoms	-0.0160	-0.1877 to 0.1557
	KOOS Pain	0.0078	-0.1532 to 0.1687
	KOOS ADL	0.0556	-0.1105 to 0.2218
	KOOS Sport	0.0056	-0.2013 to 0.2125
	KOOS QoL	-0.0375	-0.2280 to 0.1529
	OKS	-0.0256	-0.1065 to 0.0552
	Current pain (0-10 NRS)	-0.0165	-0.0405 to 0.0075
	Avg. pain last week (0-10 NRS)	-0.0042	-0.0282 to 0.0197
	SMWT (meters)	-0.7323	-1.2819 to -0.1826
	SCT up (seconds)	0.0174	-0.0097 to 0.0444
	SCT down (seconds)	0.0026	-0.0367 to 0.0419

Table 7. Simple regression models. TUT = Time-under-tension, KOOS = Knee Osteoarthritis Outcome Score, OKS = Oxford Knee Score, 6MWT = Six-minute walk test, SCT = Stair climb test

Study IV (qualitative study)

The following result section is based on text from Manuscript IV. The thematic analysis showed three main themes and nine associated sub-themes.

Themes: 1) *Physiotherapists' and orthopedic surgeons' ambivalence in their professional roles*, 2) *Orthopedic surgeons' view on exercise*, and 3) *Coordinated non-surgical and surgical care.*

Sub-themes: 1) *Supporting patient self-management is a physiotherapy core skill*, 2) *Professional role as a physiotherapist is simplified*, 3) *Skepticism towards one home-based exercise, 4*) *Skepticism towards (long-term) effect of exercise*, 5) *Different purposes of referring a patient to exercise*, 6) *Must believe in exercise as treatment for patients with severe knee OA*, 7) *Patient preferences*, 8) *Orthopedic surgeons skepticism to the content of the exercise treatment they refer to* and 9) *Responsibilities in coordinated care and engagement in the care pathway* (Table 8).

Together, the themes and sub-themes represent facilitators and barriers among the interviewed orthopedic surgeons and physiotherapists towards home-based pre-operative exercise with *one* exercise in patient eligible for KR. For elaborated results with associated quotes please see Manuscript IV (Manuscript IV).

No.	Themes	Sub-themes
1	Physiotherapists' and orthopedic surgeons' ambivalence in their professional roles	Supporting patient self-management is a physiotherapy core skill Professional role as a physiotherapist is simplified Skepticism towards one home-based exercise Must believe in exercise as treatment for patients with severe knee OA Patient preferences
2	Orthopedic surgeons view on exercise	Skepticism towards (long-term) effect of exercise Different purposes of referring a patient to exercise
3	Coordinated non-surgical and surgical care	Orthopedic surgeon' skepticism to the content of the exercise treatment they refer to Responsibilities in coordinated care and engagement in the care pathway

Table 8: Themes and associated sub-themes from the thematic analysis.

Physiotherapists' ambivalence in their professional role (Theme 1)

In summary, results from theme 1 show that, the physiotherapists perceived *the importance of providing patients with tools for self-management, the advantage of having two treatment options to meet patient preferences* and *the potential advantages of providing patients with only one exercise* as facilitators for implementing the *one* exercise in a model of coordinated non-surgical and surgical treatment. These factors support the simplified treatment approach among the physiotherapists. Contrary, the physiotherapists perceived that the home-based *one* exercise-only treatment approach *simplified their professional role, limited the contact time with patients* and *providing only <u>one</u> exercise limited use of professional skills*. This challenged the physiotherapists and created ambivalence in their professional role (Manuscript IV).

Orthopedic surgeons' ambivalence in their professional role and their view on exercise (Theme 1 and 2)

For the orthopedic surgeons, results from theme 1 and 2 show that, adhering to clinical guideline recommendations - and at the same time using clinical expertise and considering patient preferences - creates a professional dilemma. Facilitators such as *using exercise as a means to examine patient's motivation for rehabilitation*, *providing patients with a low-risk-of-complications treatment while considering the option of surgery* and *knowledge of the effect of exercise can help guide the decision of surgery* support the use of exercise as a treatment modality for patients with severe knee OA among orthopedic surgeons. Contrary, barriers among the orthopedic surgeons towards referring patients with severe knee OA to exercise were *skepticism towards the effect of exercise and especially the long-term effect in patients with severe knee OA* and *the dilemma of referring patients to exercise who are not motivated for this treatment modality*. These barriers challenge the orthopedic surgeons creating ambivalence in their professional role (Manuscript IV).

Physiotherapists and orthopedic surgeons different focus in coordinated care (Theme 3)

For theme 3, the results show that, the orthopedic surgeons and physiotherapists are preoccupied with different aspects of coordinated non-surgical and surgical care. The orthopedic surgeons focus on *what kind of treatment they refer to,* while the physiotherapists focus more on *the care pathway as a whole*. The orthopedic surgeon's express *frustration with variation in the treatment provided for the patients when they refer them to exercise in the municipality* which becomes a barrier for referring patients to exercise. The physiotherapists are positive to the *coordinated care pathway as they believe the patients are provided with quality care* which becomes a facilitator for coordinated non-surgical and surgical treatment (Manuscript IV).

Discussion

The PhD thesis investigated the dose-response relationship of pre-operative knee-extensor exercise in patients eligible for knee replacement in a coordinated care pathway of non-surgical and surgical treatment. Four studies constitute the thesis each using a different methodology to investigate the aim. Firstly, a systematic review (study I), and secondly a clinical dose-response trial (study II+III). Finally, the clinical trial and an embedded qualitative study (study IV) investigates stakeholder perspectives on a coordinated care pathway of non-surgical and surgical treatment in patients eligible for KR.

Key findings of the PhD thesis:

- The systematic review and meta-regression analysis showed no relationship between pre-operative knee-extensor exercise dosage and change in knee-extensor strength, neither before nor three months after TKA. In the meta-analyses, pre-operative exercise, including knee-extensor muscle strength exercise, increased knee-extensor strength moderately before but not three months after TKA.
- Results from the QUADX-1 trial showed no difference in change between the three groups for the primary outcome *knee-extensor strength* after 12 weeks of exercise – but group C was found to be significantly better than group B for the secondary outcomes *average knee pain last week* and *OKS*. Separalately, all three groups had significant within group changes after 12 weeks of exercise for the outcomes *average knee pain last* week, *OKS* and all *KOOS* subscales. Larger changes were observed in group C compared to group A and B, and in group A compared to group B.
- The embedded qualitative study showed that the coordinated care pathway and *one* exercise-only pre-operative exercise intervention created ambivalence in the professional role of both the physiotherapists and orthopedic surgeons. The physiotherapists were skeptical towards a too simplified exercise therapy while the orthopedic surgeons were skeptical towards the potential lack of (long-term) effects of exercise therapy in patients eligible for KR.

Knee-extensor dose-response relationship

The dose-response relationship of pre-operative knee-extensor exercise dosage on knee-extensor strength in patients eligible for KR was investigated in both the systematic review (study I) and in the QUADX-1 trial (study II+III).

The meta-regression analysis in study I suggested no dose-response relationship between pre-operative knee-extensor dosage and effect on pre- and post-operative outcomes in patients scheduled for TKA. This is especially noteworthy for the primary outcome, knee-extensor strength, as this outcome is closely related to the intervention where a higher prescribed exercise dosage would be expected to be associated with an increase in muscle strength (55). The equation we used to estimate the exercise dosage in the regression analysis may help explanation the lack of a dose-response relationship. A weakness of the equation is the estimated exercise intensity based on the Holten curve (124). Data on the actual exercise intensities might have changed the estimates. Generally, insufficent reporting of exercise program details for patients with knee OA is a well-recognized challenge (61,136,137). Another possible explanation as to why no dose-response relationship was observed could be related to the actual exercise dosage completed by the patients. In the included trials, we only have data on the *prescribed* exercise dosage. However across the included trials various levels of adherence could cloud the dose-response relationship hypothesized from the prescribed exercise dosages. Finally, substantial heterogeneity was observed in the meta-analysis questioning the comparability of the included trials – despite fulfillment of specific inclusion criteria.

In the QUADX-1 trial (study II+III), in line with the systematic review, we did not find a clear pre-operative knee-extensor dose-response relationship either (post-operative outcomes are not included for the thesis). That is, for most pre-operative outcomes, we found no differences between the three investigated exercise dosages. This was also the case for the primary outcome, knee-extensor strength. Again, this was in contrast to the hypothesis, namely that the outcome closest related to the exposure would change the most (50,55,56). However, we did see a significant difference between groups C and B for the outcomes *average knee pain last week* (NRS 0-10) (-1.1 NRS points [95% -2.2 to -0.1]) and *OKS* (4.2 OKS points [95% 0.6 to 7.8]).

As knee pain is the cardinal symptom in patients with knee OA (1,21), this difference in knee pain between group C and B is interesting. The result suggests that the exercise dosage in group C is superior for reducing knee pain to that in group B. However, what is the clinically relevance of a mean difference of -1.1 points on an 11-point scale for knee pain in patients with knee OA? For patients with chronic musculoskeletal conditions (including knee OA) Salaffi and colleagues found that a change of -1.0 points was associated with ‘slightly better’, while a change of -2.0 points was associated with ‘much better’ (138). Thus, the mean change of -1.1 points found between group C and B corresponds to a ‘slightly better’ change in knee pain, which can be considered clinically relevant.

The difference of 4.2 points in the *OKS* questionnaire between group C and B is also interesting. Various cut-offs for clinically relevant changes for the *OKS* score have been suggested. For the time period 12 months after TKA, Murray et al. suggested a limit of 3-5 points and more recently Ingelsrud et al. reported a limit of 8 points (139,140). In the context of the QUADX-1 trial, an important consideration for these cut-off points is that they are based on assessments 12 months after TKA. Firstly, TKA is a more effective treatment than exercise (40), why lower change scores are to be expected from exercise making a direct comparison between change scores after surgery and exercise difficult. Secondly, the effect of exercise in the QUADX-1 trial is assessed after 12 weeks of exercise and not after 12 months. Change scores after 12 months of exercise would be expected to be different compared to after 12 weeks. Taking these different premises into account, the difference of 4.2 *OKS* points between group C and B could be considered a clinically relevant change. In summary, the changes in *average knee pain last week* and *OKS* support the superiority of group C compared to group B. However, due to the low effect sizes these findings are not unambiguous.

The fact that no other between group differences were found for the remaining outcomes together with the modest differences between group C and B for *average knee pain last week* and *OKS* indicate no clear dose-response relationship between the three applied dosages. However, based on the results from the QUADX-1 trial it is reasonable to highlight group C as the dosage with the best potential for positive pre-operative changes in patients eligible for KR. When unblinding the trial it will be very interesting to see which exercise dosage group C was prescribed and how the objectively assessed exercise adherence corresponds to this.

Association between objectively assessed exercise completion and change in pre-operative outcomes

An inverse association was observed for *total exercise sessions completed* and change in *six-minute walk test*. No other associations between exercise completion and change in pre-operative outcomes were observed. This lack of association between objectively assessed exercise completion and change in pre-operative outcome could partly explain the inconclusive dose-response relationship observed between the three groups. The hypothesis would be that higher exercise completion would be associated with larger positive changes in outcomes (55,56). However, the results from the regression analyses reject this hypothesis. On the contrary, the results suggest that positive changes in pre-operative outcomes, as observed in the QUADX-1 trial, can be achieved with lower as well as higher total completed exercise sessions and time-under-tension (Figure 14 and 15).

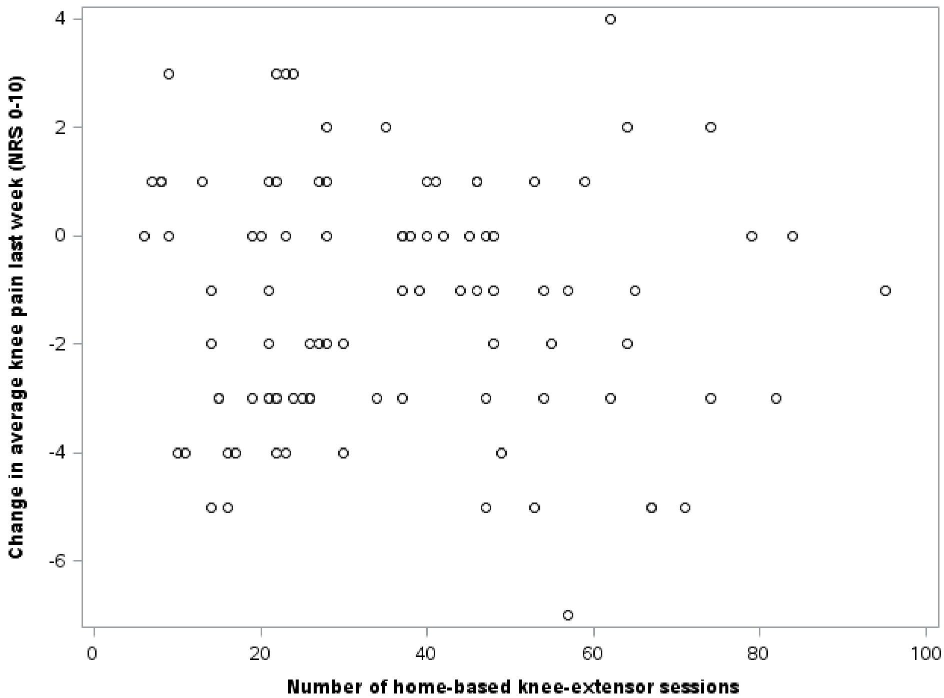

Figure 14. Plot of number of completed home-based knee-extensor exercise sessions (x-axis) against change in *average knee pain last week* (NRS 0-10) (y-axis). The individual trial participants are shown by circles.

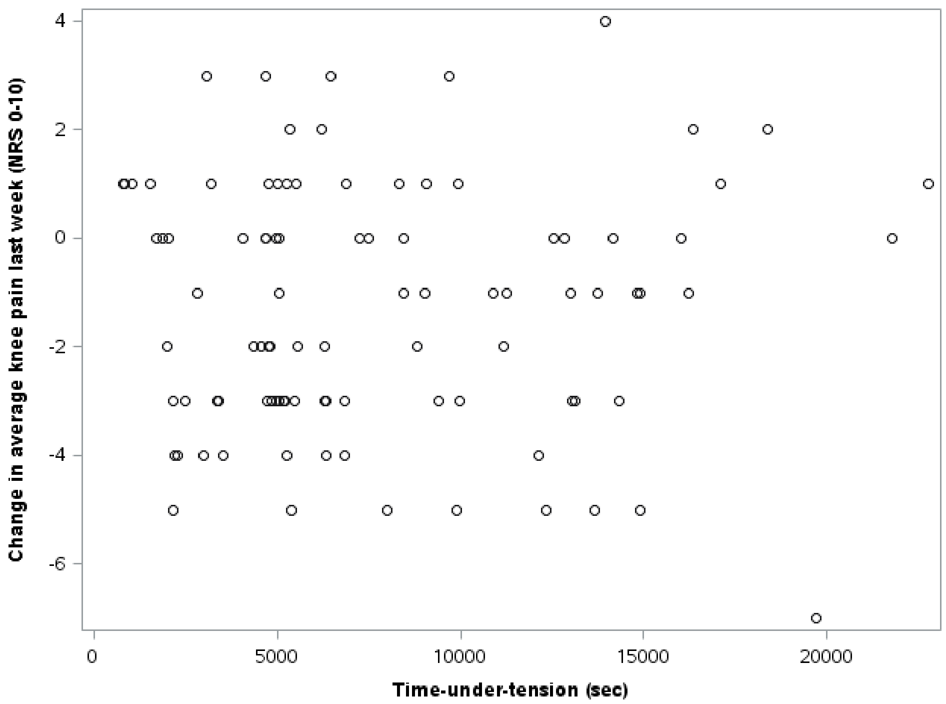

Figure 15. Plot of completed time-under-tensions in seconds (x-axis) against change in *average knee pain last week* (NRS 0-10) (y-axis). The individual trial participants are shown by circles.

Pre- and post-operative effect of pre-habilitation

Pre-operative effects of pre-habilitation

Results from both the systematic review (study I) and the QUADX-1 trial (study II+III) suggest that there is an exercise potential before surgery in patients eligible for KR. This is in contrast to a previous systematic review concluding no effect before surgery of pre-operative exercise in patients scheduled for total knee arthroplasty (61). In the meta-analysis we identified an effect of pre-operative exercise before TKA with a moderate increase in knee-extensor muscle strength (SMD 0.50 [0.12 to 0.88]). When analyzing the patients from the QUADX-1 trial as one sample, we found a positive within group increase in knee-extensor muscle strength from baseline to after 12 weeks of exercise (0.13 Nm/kg [95% 0.07 to 0.19]). The three groups had a within group knee-extensor strength changes of A) 0.11 Nm/kg (95% -0.007 to 0.19), B) 0.15 Nm/kg (95% 0.04 to 0.25) and C) 0.12 Nm/kg (95% 0.02 to 0.22). In the protocol for the QUADX-1 trial we set the minimal clinically important difference for change in knee-extensor strength to 0.15 Nm/kg (108). Thus, only group B had a clinically relevant within group change in knee-extensor strength. Interestingly, group B was the group with the smallest changes in the secondary outcomes (see below). This contrasts the hypothesis that larger improvements in knee-extensor muscle strength would be associated with larger changes in other outcomes (e.g. knee pain) as increased knee-extensor strength can mediate other health effects (50).

In the meta-analyses, the significant effect observed for increase in knee-extensor muscle strength was not seen in any other pre-operative outcomes, but there was a tendency for improved *knee pain* and *function*. In the QUADX-1 trial we found clinically relevant within group improvements for the whole sample in the following secondary pre-operative outcomes; *OKS*, *average knee pain last week* and all *KOOS subscales*. Looking at the three groups separately, larger changes were observed in group C compared to group A and B, and in group A compared to group B. Group C showed a clinically relevant within group change in most outcomes. For example, group C had within group change scores >10 points in all *KOOS subscales*. Though, as discussed above there was no clear significant dose-response relationship between the three groups. For the descriptive results of the secondary outcome *need for surgery*, there was a pattern of more patients answering 'yes' in group B compared to group C (15 vs. 9) and more patients answering 'no' in group C compared to group B (23 vs. 13). Again, group C stands out as the group with the exercise dosage of most potentiale for positive pre-operative changes in patients eligible for KR. It should be noted that this was a secondary descriptive analysis, and that the trial was not designed or powered for this specific analysis.

Interestingly, the results from the meta-analysis and the QUADX-1 trial on the effect of pre-operative knee-extensor exercise is somewhat conflicting. In the meta-analysis, we found a pre-operative effect on knee-extensor muscle strength but not on the secondary outcomes while the opposite was found in the QUADX-1 trial. The large heterogeneity in the meta-analyses could be part of the explanation for this discrepancy. A potential explanation for the lack of significant effects on pre-operative knee pain and function in the meta-analyses could be related to the moderate effect found on knee-extensor muscle strength. Recently, Bartholdy et al. suggested a minimum increase of 30% in knee-extensor strength (large effect) needed to affect outcomes on knee pain and disability in patients with knee OA – this could in part explain the results from the meta-analyses where a moderate effect on knee-extensor strength was found but no effect was found for knee pain and function (74). However, the large increase in knee-extensor strength suggested by Bartholdy et al. is in contrast to the results found in the QUADX-1 trial with barely no clinically relevant within group changes in knee-extensor muscle strength but with clinically relevant changes in secondary outcomes, i.a. knee pain. These contrasting effects found in the QUADX-1 trial challenge the hypothesis that an increase in knee-extensor muscle strength leads to improvements in e.g. knee pain and function and suggest that knee-extensor exercise can improve knee pain and function without large improvements in knee-extensor muscle strength. Another potential explanation is that patients eligible for KR have an inactive lifestyle due to their knee condition (141,142). Inactive lifestyle can lead to decrease in physical ability and muscle strength leaving a large potentiale for improvement (55,143–145). Thus, potentially patients eligible for KR do not need large exercise dosages to achieve strength improvement (146). Similarly, equivocal results of the effect of knee-extensor exercise on knee pain and function in patients with knee OA has been reported by Hall et al. where an increase in knee-extensor strength only partially affected improvement in symptoms (50). A potential explanation for this will be discussed below in the paragraph *Exercise induced hypoalgesia*.

Post-operative effects of pre-habilitation

The meta-analyses showed no significant effect on post-operative outcomes three months after TKA. Only the outcome measure *function* showed a tendency for a positive effect of pre-operative knee-extensor exercise. The post-operative effects in the QUADX-1 trial are omitted from the thesis as mentioned previously. Though, as will be discussed below, 79 (67.5%) of the 117 patients completing 12 weeks of home-based exercise in the QUADX-1 trial choose to postpone surgery. Interestingly, the lack of post-operative effect observed in the meta-analyses and the large number of patients postponing surgery in the QUADX-1 trial combined with the positive pre-operative effects found in both the meta-analysis and the QUADX-1 trial suggest that knee-extensor exercise before surgery is effective in improving outcomes before but not after surgery in patients eligible for KR. These results are in line with recent findings showing an effect of pre-operative exercise on outcomes before but not after KR (39,147).

Treatment decision after home-based exercise

In the QUADX-1 trial, following the 12 weeks of home-based knee-extensor exercise, the patients' *need of surgical treatment* was re-assessed by the patient and an orthopedic surgeon. Seventy-nine (67.5%) of the 117 patients completing the exercise intervention postponed surgery, 32 (27.4%) choose surgery and six (5.1%) wanted surgery but surgery was contra-indicated. The number of patients postponing surgery was surprising and higher than we expected. Prior to the initiation of the QUADX-1 trial, members of the research group expected that between 0% and 25%

of patients would postpone surgery. Since the initiation of the QUADX-1 trial, similar proportions of patients eligible for KR postponing surgery after exercise therapy has been reported (39).

The proportion of patients postponing and choosing surgery across the three groups was equal with no significant difference in treatment decision observed. This indicates that the decision to postpone surgery could be independent of prescribed exercise dosage and the inherent effect. It should be noted that this was a post hoc analysis, and that the trial was not designed or powered for this specific analysis. The logic hypothesis, in which you would expect a larger proportion of patients experiencing symptoms relief to postpone surgery, is in contrast to the results. For example, as a consequence of the dose-response effect observed for group C vs. group B for the pre-operative outcomes *average knee pain last week* and *OKS*, one would expect a larger proportion of patients in group C compared to group B to postpone surgery. Though not significant, there were more patients postponing surgery in group C compared to group B (30 vs. 24) and fewer patients choosing surgery (7 vs. 13). Again it should be noted that the trial was not designed or powered to investigate this.

A potential explanation for the equal distribution of patients postponing surgery among the three groups could be the applied ‘model’ of coordinated non-surgical and surgical care. In this ‘model’, the patients’ need for surgical treatment is re-evaluated following exercise by the patient and an orthopedic surgeon. This re-evaluation of treatment and change in symptoms combined with additional attention from an orthopedic surgeon could facilitate the patients’ decision to postpone surgery (92–94). That is, patients who are eligible for surgery and who are informed of this treatment option, but firstly referred to exercise and then re-evaluated, are both provided with an alternative treatment while also given extra time to consider the option of surgery. An explanation to the result is that, regardless of prescribed exercise dosage, exercise treatment combined with re-evaluation of the effect of non-surgical treatment can facilitate a shared decision on future treatment. This corresponds well with a facilitator towards exercise therapy mentioned by the orthopedic surgeons during the interviews: An orthopedic surgeon expressed that exercise was a good alternative for patients who needed time, ‘a breathing space’, to consider the treatment option of surgery.

Exercise induced hypoalgesia

Hypothetically, an increase in knee-extensor muscle strength, as a results of resistance training, should lead to a decrease in knee pain and an improved functional performance, which would lead to improved quality of life and possibly the postponement of surgery (Pathway A, Figure 13) (50). However, we observed small, not clinically relevant, changes in knee-extensor strength in the QUADX-1 trial. Despite this lack of clinically relevant changes in knee-extensor strength, we found clinically relevant changes in e.g. *knee pain* (Whole sample: 9.9 *KOOS* points and -1.2 *NRS* 0-10 points), *quality of life* (Whole sample: 8.2 *KOOS* points) and 67.5% of the patients postponed surgery. This pattern of improvement in e.g. knee pain, independent of change in knee-extensor strength, could be explained by 'exercise induced hypoalgesia' (EIH) (Pathway B, Figure 13).

Exercise induced hypoalgesia is defined as a decreased sensitivity to painful stimuli, e.g. knee OA, after exercise (31,148). Recent reviews conclude that muscle contractions during strength- and aerobic exercise cause EIH in patients with OA and that exercise is an effective treatment for pain in patients with OA (149,150). Specifically related to the intervention in the QUADX-1 trial, previous studies have found that exercise interventions, including knee-extensor strength exercises, for patients with knee OA improve knee pain and function (151–153). This supports the notion of a positive effect of exercise on symptoms in patients with knee OA independent of change in knee-extensor strength.

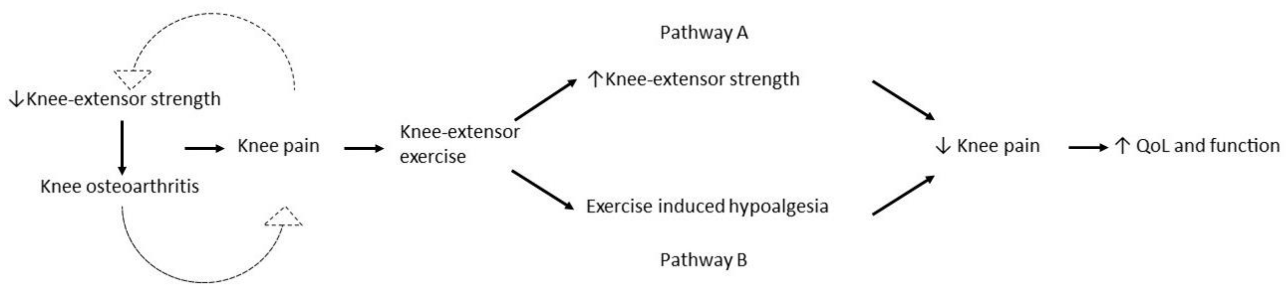

Figure 13. Hypothetical model of how knee-extensor exercise can affect knee OA related symptoms.

Scenarios of exercise dosage in group A, B and C

Based on the hypothesis presented in the protocol paper for the QUADX-1 trial (4 sessions/week being superior to 2 and 6 sessions/week, and 6 sessions/week being superior to 2 sessions/week), group C would represent 4 sessions/week, group A 6 sessions/week and group B 2 sessions/week. Group C has the largest within group changes for all outcomes, though these are not significantly different from the changes in group A. This scenario would support the hypothesis that 4 sessions/week is optimal with two extra sessions (6 sessions/week) having no additional benefit. Group C performed significantly better than group B for the outcomes *average knee pain last week* and *OKS*, supporting that 4 sessions/week is superior to 2 sessions/week. Results from the regression analyses suggest no association between completed exercise and change in outcomes. This challenges the above hypothesis and suggests that group C is either 2 or 6 sessions/week and *vice versa* for group B and A.

How results from the QUADX-1 trial can mitigate ambivalence in the professional roles of the physiotherapists and orthopedic surgeons

The identified barriers on "effect of *one* exercise", "quality of unsupervised exercise" and "limited contact time between physiotherapists and patient" mentioned by the physiotherapists could be mitigated when the physiotherapists are presented with the results of the QUADX-1 trial. That is, the results suggest that the simplified exercise treatment is effective in improving the patients' symptoms. Additionally, implementation of the unsupervised exercise treatment as a treatment option could facilitate that physiotherapy resources in the municipalities were organized differently and canalized towards patients with lower resources and with more need of supervision. This complies with another barrier mentioned by the physiotherapists – that the simplified exercise treatment provided in the QUADX-1 trial is not a good treatment option for all patients. The home-based *one* exercise-only intervention is a good alternative to patients who have a busy daily schedule, patients who cannot afford or are not interested in attending formal group exercise sessions at a clinic at fixed times, but not for those in need of e.g. supervision (154). Thus, the home-based exercise intervention should not replace outpatient group-based exercise sessions but represent an alternative option. Also, having two exercise therapy options provides better alternatives for the patients. As part of the PREHAB-KR project patients were also interviewed regarding their experiences with the intervention in the QUADX-1 trial. This data is not analyzed yet and is not part of the thesis. When analyzed these data will provide further information on the utility of the home-based *one* exercise-only intervention and the coordination of non-surgicala and surgical treatment.

The skepticism towards "the effect of exercise therapy in patients eligible for KR" mentioned by the orthopedic surgeons could be mitigated when presented with the positive changes in clinical outcomes. The results could also facilitate adherence to guideline recommendations of patients trying non-surgical treatment before surgery. Further, the results could ease the ambivalence in the professional role of referring patients to a treatment which effectiveness they are skeptical towards. Orthopedic surgeons provide a one-time treatment (surgery) with a long-lasting effect (155). In contrast, exercise therapy is only effective when maintained over time (21,87,156). This is similar to the use of insulin in patients with diabetes who also have to continue taking insulin to sustain the effect (157). This is an interesting and important point to communicate to orthopedic surgeons who are skeptical towards the effect, and especially the long-term effect, of exercise in patients eligible for KR. Thus, when evaluating the effect of exercise therapy, and if there is an effect, it is imperative to communicate to the patient the importance of continuing exercising to sustain the effect over time (21). The responsibility of communicating this to the patient relies both on physiotherapists and orthopedic surgeons (158,159). As a follow-up project to the QUADX-1 trial we are currently performing annual assessments with i.a. questions related to the exercise behavior of the patients.

An enhanced care pathway facilitating shared decision-making

Shared decision-making

The results from the systematic review and the QUADX-1 trial suggest that patients with severe knee OA, who are eligible for KR, can benefit from pre-operative exercise therapy before surgery. However, it does not seem to affect post-operative outcomes. Thus, if surgery is pre-planned and will be completed regardless of the effect of pre-operative exercise, then pre-operative exercise is essentially a waste of both the patient's and health care professional's time and resources. At least when evaluating clinical post-operative outcomes like knee pain, function and knee-extensor muscle strength.

The positive effect of pre-operative exercise on symptoms in patients eligible for KR contrast with barriers identified in the qualitative study. The orthopedic surgeons expressed skepticism towards the effect of exercise in this patient population and the physiotherapists were skeptical towards the effect of unsupervised exercise with *one* exercise. This points towards two interesting points of discussion – 1) whether pre-operative exercise is useful in pre-habilitation in patients eligible for KR and 2) whether exercise is effective as a “stand alone” treatment and could be used in shared decision-making.

Within the ERAS paradigm it is assumed that exercise therapy before planned surgery (pre-operative exercise) is followed by surgery (62–64,70,71). However, instead of being a predetermined treatment trajectory, pre-operative exercise therapy could be considered as a part of the shared decision-making process when planning a care pathway (23,67,79). A more optimal way of combining the two treatment options, exercise therapy and KR, could be to incorporate information on the effect of exercise therapy to enhance shared decision-making. For an example, a patient eligible for KR could be referred to exercise therapy and if this was effective (i.e. reduced the patient’s symptoms sufficiently), then continued exercise therapy should be encouraged and KR postponed for when or if exercise therapy becomes insufficient. On the contrary, if exercise therapy was ineffective, then KR might be the best treatment option. A treatment trajectory with exercise therapy being tried out before KR also complies with guideline recommendations (18,37,79).

Enhanced care pathway

The positive change in outcomes and the high number of patients postponing surgery after completing home-based exercise in the coordinated care pathway applied in the QUADX-1 trial, suggest improved care for patients eligible for KR. The coordinated care pathway ensures that the patients are provided with non-surgical treatment before surgery according to guideline recommendations and the effect of the non-surgical treatment is evaluated and the need of surgery re-evaluated. In this coordinated care pathway, both the patient and the orthopedic surgeon have a better base of information enabling both to better decide on the most appropriate treatment going forward. In a care pathway without the option of exercise and subsequent re-evaluation, more patients who might have postponed this treatment might undergo surgery. Besides providing a less invasive treatment it frees up space on the surgical waiting list for patients in greater need of surgery and thus indirectly affects other patients to a timelier care pathway. Finally, the home-based exercise used in the QUADX-1 trial provides patients with a tool enabling self-management of knee OA related symptoms. This increases the chance of maintained successful treatment while complying with recommendations of patient self-management in non-surgical treatment of patients with knee OA (37,81,86,160).

Limitations

Limitations in the QUADX-1 trial (study II+III) will be discussed in the below paragraph. Limitations pertaining to the systemativ review (study I) and the qualitative study (study IV) are discussed in Manuscript I and IV, respectively.

Limitations in the QUADX-1 trial

The QUADX-1 trial has some limitations, which must be taken into consideration when interpreting the results. Pertaining to the primary outcome, it is acknowledged that knee-extensor muscle strength is not a highly clinically relevant outcome for patients being a surrogate measure of e.g. physical function and on the “body functions and structures” level of the ICF model (161). However, when investigating a dose-response relationship, it is relevant to have an outcome closely related to the exposure while also being an outcome that can mediate other health effects (50,55,56). Further, knee-extensor muscle strength is related to the development and progression of knee OA (42,162). As a consequence of the dose-response design there was no control group limiting the conclusions that can be made based on the effect of the knee-extensor exercise. Neither the physiotherapists nor the patients were blinded to the intervention as this was not possible (163,164). But the patients were blinded to the other exercise dosages and the trial hypothesis. Due to the “active” nature of the intervention, there is a risk of selection bias. That is, there is a risk that the included patients mainly represent patients who are motivated for exercise and who are also reluctant towards surgery (165–167). This limits the external validity and the inferences that can be made for the entire knee OA population. Further, the risk of selection bias could affect the outcome *need for surgery*, as patients more motivated for exercise could be more inclined to answer ‘no’ to needing surgery. The large number of patients postponing surgery could confirm this bias. However, the positive pre-operative effects could also explain the decision to postpone surgery. We expected a drop-out rate of 10%, but a larger proportion of patients (16.4%, n=23) dropped-out or had missing data. The main reason for drop-out was the adverse event knee pain. This questions the applicability of exercise in all patients eligible for KR. Being able to identify these patients would be a valuable tool in the clinic.

Conclusion

In conclusion, results from the meta-analyses and the QUADX-1 trial show no clear dose-response relationship between pre-operative knee-extensor exercise dosage and change in outcomes before or after surgery in patients eligible for KR. The results indicate that pre-operative knee-extensor strengthening exercise improves outcomes before surgery in patients eligible for KR. In contrast, results from the systematic review show that pre-operative exercise does not seem to improve outcomes after surgery. Results from the QUADX-1 trial support the effect of *one* exercise-only knee-extensor exercise before potential surgery in patients eligible for KR with improvement in i.a. the cardinal symptom, knee pain. This improvement in outcomes before surgery was independent of prescribed exercise dosage. However, there was a tendency for dosage C to be superior to dosage B. Overall, all three exercise dosage groups improved their outcomes after exercise but exercise dosage C had the largest improvements. In speculation, dosage C could be 6 session/week and dosage B could be 2 sessions/week. The finding that pre-operative knee-extensor exercise improves symptoms before potential surgery is further supported by the large number of patients postponing surgery after knee-extensor exercise in the QUADX-1 trial. In the imbedded qualitative study we found that the pre-operative *one* exercise-only intervention was associated with barriers creating ambivalence in the professional role of both the physiotherapists and the orthopedic surgeons. These barriers, and the associated ambivalence in the professional role are important to consider when evaluating the coordinated non-surgical and surgical care pathway.

Perspectives

The results presented in this thesis are important to patients eligible for KR, clinicians (orthopedic surgeons and physiotherapists) working with these patients and for stakeholders informing decisions of health care and structuring the healthcare system. The results suggest that the concept of pre-habilitation (with exercise) is not applicable for patients who are eligible for KR as the effect of exercise before surgery does not seem to affect outcomes after surgery – effectively devaluating the premise of pre-habilitation in patients eligible for KR. Contrary, the results indicate that exercise in patients eligible for KR is effective in relieving knee OA related symptoms to a degree where a large number of patients choses to postpone surgery. This suggests that exercise before surgery in patients eligible for KR should primarily be used to evaluate the need for surgery rather that to improve outcomes after surgery. Thus, exercise before surgery should be included as a means in the shared decision-making consultation where the optimal care pathway for each patient in planned.

As mentioned by an orthopedic surgeon in the qualitative study, orthopedic surgeons effectively act as gate-keepers for referring patients to pre-operative exercise therapy (25). Likewise, the orthopedic surgeons are gate-keepers for facilitating shared decision-making as they are in a position to provide information to patients on all their treatment options and care pathway. Therefore, the results from both the systematic review and the QUADX-1 trial are important to communicate to orthopedic surgeons, especially those skeptical towards exercise therapy in patients eligible for KR. Adding to this, patients take more active part in their treatment when informed of their treatment options (93).

The orthopedic surgeons were skeptical towards the effect of exercise therapy in general in the population of patients eligible for KR, especially in the long term and the physiotherapists were skeptical towards the effectiveness and quality in an exercise intention with *one* home-based exercise. The short-term effectiveness of the one exercise-only intervention is supported by the improvements in outcomes and the large number of patients postponing surgery. In the time frame of this thesis, long-term follow-ups have not been possible. However, as a follow-up project (the QUADX-1 trial follow-up) we are following all the patients from the QUADX-1 trial as a cohort with annual assessments. The purpose is to document for how long patients keep postponing surgery, if they exercise, how they exercise and whether there is an association between their exercise habits and postponement of surgery.

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Appendix 1

Co-morbidities disqualifying six patients for surgery after exercise.

1) Smoker, reduced lung function (diagnosed with chronic obstructive pulmonary disease) and obesity.
2) Acute neurological and urological diagnoses.
3) Obesity.
4) Acute neurological diagnosis.
5) Referred to further diagnosing.
6) Personal challenges.

Papers
And
Manuscripts

Manuscript I

The relationship between pre-operative knee-extensor exercise dosage and effect on knee-extensor strength prior to and following total knee arthroplasty: A systematic review and meta-regression analysis of randomized controlled trials

Rasmus Skov Husted, Carsten Juhl, Anders Troelsen, Kristian Thorborg, Thomas Kallemose, Michael Skovdal Rathleff and Thomas Bandholm

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Title

The relationship between pre-operative knee-extensor exercise dosage and effect on knee-extensor strength prior to and following total knee arthroplasty: A systematic review and meta-regression analysis of randomized controlled trials

Rasmus Skov Husted (RSH)[1,2,3]*, Carsten Juhl (CJ)[4,5], Anders Troelsen (AT)[3], Kristian Thorborg (KT)[2,6], Thomas Kallemose (TK)[1], Michael Skovdal Rathleff (MSR)[7,8] and Thomas Bandholm (TB)[1,2]

[1]Clinical Research Centre, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

[2]Physical Medicine & Rehabilitation Research - Copenhagen (PMR-C); Department of Physical and Occupational Therapy; Clinical Research Centre; Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

[3]Clinical Orthopedic Research Hvidovre (CORH), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

[4]Department of Physiotherapy and Occupational Therapy, Copenhagen University Hospital, Herlev and Gentofte, Denmark

[5]Research unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

[6]Sports Orthopaedic Research Center – Copenhagen (SORC-C), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

[7]Center for General Practice at Aalborg University, Aalborg, Denmark

[8]Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark

E-mail addresses: CJ (cjuhl@health.sdu.dk), AT (a_troelsen@hotmail.com), KT (kristian.thorborg@regionh.dk), TK (thomas.kallemose@regionh.dk), MSR (misr@hst.aau.dk), TB (thomas.quaade.bandholm@regionh.dk)

*Primary investigator and corresponding author. Clinical Research Centre (Section 056), Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Denmark. Mail: rasmus.skov.husted@regionh.dk

Abstract

Objective

The aim of this systematic review was to evaluate the relationship between knee-extensor strength exercise dosage in pre-operative exercise intervention and the effect on knee-extensor muscle strength prior to and following TKA.

Design

A systematic literature search was performed including RCT´s evaluating the effect of pre-operative exercise prior to and following TKA. Meta-regression analysis was performed to evaluate the dose-response relationship between exercise dose and the pooled effect, measured as standardized mean difference (SMD).

Results

Twelve trials with 616 patients were included. Meta-regression analysis showed no relationship between pre-operative knee-extensor exercise dosage and change in knee-extensor strength neither prior to (slope 0.0005 [95%CI -0.007 to 0.008]) or three months following TKA (slope 0.0014 [95%CI -0.006 to 0.009]). Prior to TKA, a moderate effect favoring pre-operative exercise for increase in knee-extensor strength was found (SMD 0.50 [95%CI 0.12 to 0.88]), but not at three months following TKA (SMD -0.01 [95%CI -0.45 to 0.43]).

Conclusion

We found no relationship between pre-operative knee-extensor exercise dosage and change in knee-extensor strength. Pre-operative exercise including knee-extensor muscle strength exercise increased knee-extensor strength moderately prior to but not three months following TKA.

Protocol registration

PROSPERO ID (CRD42018076308) (http://www.crd.york.ac.uk/PROSPERO/)

Key words

Knee osteoarthritis, dose-response, exercise therapy, knee-extensor muscle strength, total knee arthroplasty

Introduction

Patients diagnosed with knee osteoarthritis (OA) report knee pain, decreased physical function and quality of life [1]. Physically, patients with knee OA are characterized by low knee-extensor muscle strength which is associated with decreased physical function, independent of knee pain [2]. Further, patients diagnosed with severe knee OA awaiting total knee arthroplasty (TKA) have 35% lower knee-extensor muscle strength compared to age-matched controls [3]. Additionally, 60-80% of their pre-operative knee-extensor muscle strength is lost shortly (days to weeks) after surgery, likely due to arthrogenic muscle inhibition [4–6].

Pre-habilitation is defined as an intervention (e.g. exercise therapy) aiming to improve the physical capacity of a patient prior to a stressful event (e.g. surgery), so that the patient better can withstand the negative consequences of surgery [7,8]. Considering the population of patients awaiting TKA, we see two arguments for pre-habilitation: First, the recovery challenges following TKA include low knee-extensor muscle strength, knee pain, low physical function and long time-to-recovery [9,10]. This may make pre-habilitation important for optimization of physical function in patients awaiting TKA and may enhance recovery after surgery [10–12]. Second, when assessing the need for surgical or non-surgical treatment, information on changes in knee OA symptoms during pre-habilitation is valuable in the shared decision-making process [7,13]. Pre-habilitation with a positive effect on knee OA symptoms supports patient's self-management of their knee OA condition - potentially postponing the need for surgery [14,15]. However, the optimal pre-habilitation knee-extensor strength exercise dosage remains unclear.

Systematic reviews published within the last 15 years on the effect of pre-habilitation on post-operative outcomes in patients undergoing TKA have found only moderate-to-small or no clinically relevant improvements in knee pain, performance-based function and muscle strength outcomes [16–26]. Despite a potential for efficacy of pre-habilitation in patients eligible for TKA there is a scarcity of robust dose-response evidence [27]. Recent trials by Calatayud et al. and Skoffer et al. investigating pre-habilitation prior to TKA found clinical relevant effects prior to and following TKA on knee-extensor muscle strength, knee pain and physical function outcomes [28,29]. The trials by Calatayud et al. and Skoffer et al. differ from previous trials by prescribing large pre-habilitation exercise dosages targeting the knee-extensor muscles with a clear reporting of the exercise intensity (repetitions relative to 1 repetition maximum (RM)) [28,29]. The most recent systematic review included the trials by Calatayud et al. and Skoffer et al. in their meta-analysis [23]. However, the potential larger effect in these trials, due to larger exercise dosages, could be overlooked in a meta-analysis, blurring a potential dose-response relationship. This calls for an analysis of the dose-response relationship.

Objectives

The aim of this systematic review was to evaluate the dose-response relationship between knee-extensor muscle strength exercise dosage in pre-habilitation and the effect on knee-extensor muscle strength (primary outcome), performance-based function and patient-reported outcomes (secondary outcomes) prior to and following TKA in patients with severe knee OA.

We hypothesized a positive relationship between knee-extensor muscle strength exercise dosage and increase in knee-extensor strength, performance-based function and patient-reported outcomes prior to TKA and less decline following TKA.

Methods

Protocol and registration

The systematic review was conducted in accordance with the guidelines in the Cochrane Handbook [30]. The protocol was pre-registered on PROSPERO (CRD42018076308) 4/1-2018. The protocol followed the PRISMA-P guideline [31] and the review is reported according to the PRISMA guideline [32].

Eligibility criteria

Only randomized controlled trials (RCT's) with the following characteristics were included: Patients scheduled for total knee arthroplasty (TKA) diagnosed with knee OA according to the American College of Rheumatology criteria [33] and radiographic verified knee OA classified as Kellgren-Lawrence classification ≥2. The exercise intervention was "resistance training" as defined in the Medline Medical Subject Heading (MeSH-term) [34] and had to take place prior to surgery, i.e. pre-habilitation. The exercise intervention had to comprise at least one strengthening exercise primarily targeting the knee-extensor muscles (e.g. sitting knee-extension or leg-press). The control groups should either be described as receiving: a lower exercise dosage than the intervention group, exercise not defined as resistance training, no intervention, “care as usual”, placebo control or patient education. All included trials had to have an assessment of the outcome knee-extensor muscle strength and to have an outcome assessment prior to surgery. Trials with follow-up outcome assessments after surgery were also included to assess whether effects following pre-habilitation improved outcomes following TKA (secondary analysis). No limitation in follow-up time was applied.

Information sources and Search

A systematic literature search was performed 27/8-2019 in the following databases; Medline via PubMed, Embase via OVID, CINAHL via EBSCO, and CENTRAL. The literature search included medical subject headings (e.g. MeSH in PubMed) and text words related to “knee OA” and “exercise therapy”. The PEDro database was also searched. To further ensure literature saturation, we scanned the reference lists of the included trials for relevant references. Only trials reported in English, Danish, Norwegian, Swedish, German or Dutch were included. Language, however, was not a limitation in the search and no limit on date was applied. The search strategy was created by RSH, CJ and TB and performed by RSH. The search string for Medline is available online. This search strategy was adapted to the other databases. To limit the search to RCTs, the *Cochrane Highly Sensitive Search Strategy for identifying randomized trials* was applied (see above link).

Study selection

All identified titles and abstracts were assessed for eligibility by two independent reviewers (RSH and TB) based on the in- and exclusion criteria. All trials judged eligible by at least one reviewer were obtained in full text and assessed in detail according to the eligibility criteria by the same two reviewers. In case of disagreement on eligibility, a third researcher was consulted (MSR).

Data collection process

Double data-extraction was applied with RSH and MSR independently extracting the pre-defined data (see below data items). The extracted data was entered the online software program covidence.org and cross-checked for differences in data-extraction. We contacted the corresponding author of Walls et al. [35] regarding access to raw data as the published data was only presented in figures. We received no response and, thus, we extracted data from the figures using appropriate software.

Data items

The following data items were extracted from the included trials: *Trial-related data:* Year of publication, authors, design, registration (prospectively or not), follow-up time-points and number of patients allocated to intervention and control group. *Patient related data:* Sex, age, body mass index (BMI), baseline level of knee pain and radiographic severity of knee OA. *Intervention-related data:* Type and number of knee-extensor exercises, length of intervention (weeks), number of exercise sessions per week, number of sets per exercise session, number of repetitions per set, intensity of the exercise (repetition maximum (RM/% of 1 RM)) and a description of other exercises in the intervention. The Consensus on Exercise Reporting Template (CERT) [36] was used as the template for data extraction of exercise related data, and supplement by the mechanobiological exercise descriptors suggested by Toigo and Boutellier [37]. For this systematic review prescribed exercise volume was investigated, not the actual completion of exercise (adherence). *Control group data:* A brief description of the intervention. *Outcome-related data:* Primary outcome; knee-extensor strength (e.g. isometric or isokinetic measurements). Secondary outcomes; knee pain, patient reported function (e.g. activities of daily living), knee-related performance-based function (e.g. ability to ascend a flight of stairs) and adverse events.

Risk of bias in individual trials

The risk of bias in the included trials was assessed using the Cochrane *Risk of Bias Tool* [38]. The assessment was completed independently by two reviewers (RSH and TB). In case of disagreement a third reviewer was used as an arbitrator (MSR). Each of the following domains was evaluated as to whether they were adequate (low risk of bias), unclear or inadequate (high risk of bias); sequence generation, allocation concealment, blinding of participants, personnel and outcome assessor, incomplete outcome data, selective outcome reporting and other sources of bias.

Summary measures

Effect size on continuous data are presented as standardized mean differences (SMD) with 95% confidence intervals (CI). The SMD was estimated as the difference between final scores in the intervention and control groups divided by the pooled standard deviation (SD), allowing pooling and comparison of outcomes across the individual trials according to the Cochrane Collaboration [30]. The mean scores and SD's were extracted where available or otherwise calculated from CI's or standard errors (SE) [30] (dataset and code available in supplementary material 3 and 4). The effect size of the SMD was interpreted as following; 0.2 = small, 0.5 = moderate and >0.8 = large (Cohen's d) [39]. All effect sizes were adjusted with the Hedges bias correction to Hedges g [30]. When interpreting the summary measures the result of the risk of bias assessment is taken into consideration. For example, trials reporting large effect sizes but with a high risk of bias will not be given a high clinically-relevant effect.

Synthesis of results

Between-trial inconsistency (heterogeneity) was assessed using the I^2 statistics. I^2 statistics of 30-60% were defined as moderate heterogeneity. All outcomes were combined and analyzed using Stata statistical software version 11.0 and followed the statistical guidelines from the Cochrane Collaboration [30]. If tests of heterogeneity were I^2 <30% the fixed effect model was used. If statistical heterogeneity was observed (I^2 >30%) the random effects model was chosen.

Risk of bias across trials

In case of small trials with a large effect (risk of small study bias), we conducted a funnel plot, Eggers regression test and the "trim and fill" method to investigate this. The results of the meta-analyses are presented in forest-plots. In case of high levels of heterogeneity (I^2 >30%) between the results in the included trials, trial characteristics are analyzed by meta-regression to investigating the impact on the heterogeneity (reduction in tau-squared (T^2)).

Additional analyses

Meta-regression analyses investigating the effect of pre-operative knee-extensor exercise dosage on knee-extensor strength, knee pain, patient reported function and knee-related performance-based function prior to and 3 months following TKA was performed. Previous systematic reviews have examined the influence of single exercise dosage descriptors (e.g. number of weeks or sessions) on knee pain and function in patients with mild-to-severe knee OA [40,41]. However, when investigating single exercise descriptors there is a risk of leaving out important information related to the total exercise dosage prescribed. To account for as many relevant exercise dosage descriptors as possible we defined knee-extensor exercise dosage as:

$$\text{Knee-extensor exercise dosage} = (knee * w * s * se * r) * \frac{i}{r}$$

Abbreviation explanation: knee = number of knee-extensor exercises, w = weeks, s = sessions per week, se = sets per session, r = repetitions per set, i = exercise intensity (estimated % 1 RM)

In trials where the exercise intensity was not reported (10 of 12 included trials) the number of repetitions was used to estimate the exercise intensity, according to the Holten curve (e.g. 11 repetitions = exercise intensity corresponding to 11 RM = 80% of 1 RM) [42]. The *total number of repetitions* (knee*w*s*se*r) was multiplied with the *exercise intensity* divided by *repetitions per set* (i/r) to normalize the exercise dosage to the 1 RM scale/the Holten curve [42]. The impact of co-variates was evaluated in a series of meta-regression analyses adjusted for each one of the co-variates age, sex, BMI, knee pain at baseline, knee-extensor strength at baseline and whether the control group received an active (exercise therapy) or passive (e.g. information) intervention of the lower extremities.

Results

Study selection

After removing duplicates, 4550 potentially relevant articles were identified. Following title and abstract screening, 4510 articles were excluded, and 40 articles were read full text. Twenty-eight articles were excluded as they did not meet the inclusion criteria and 12 articles were included for analysis (Figure 1).

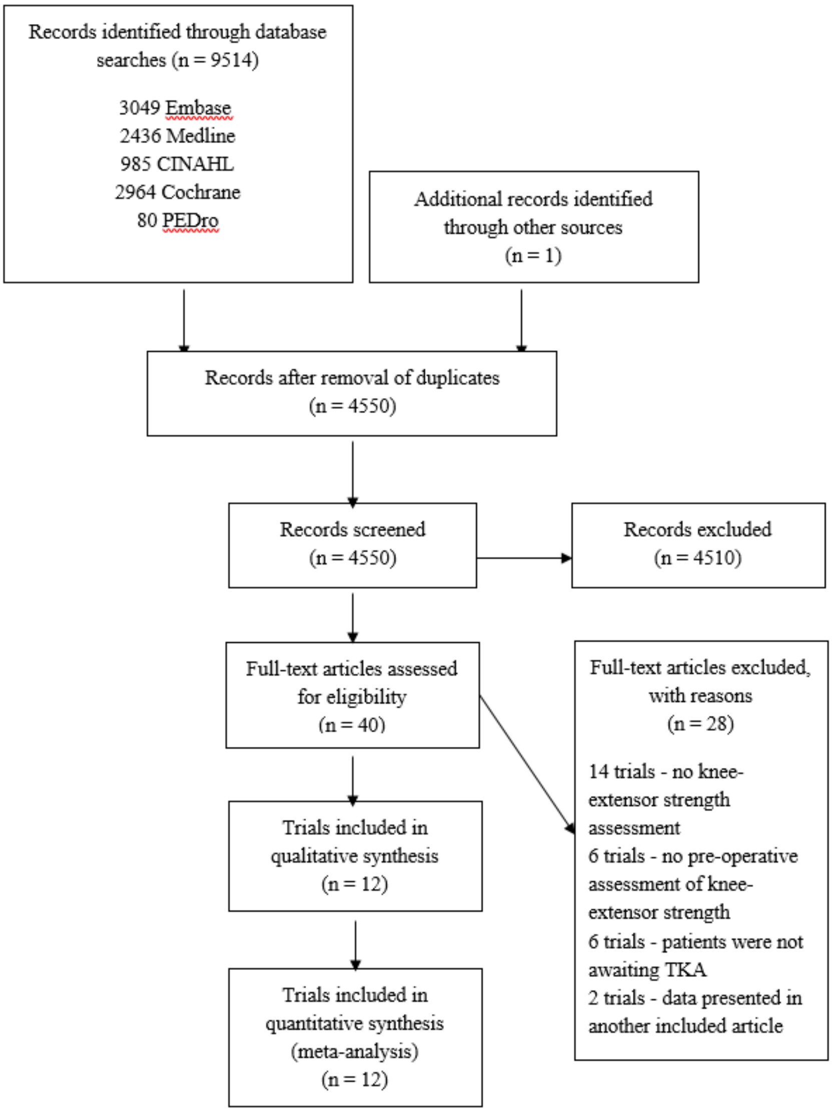

Figure 1. Flowchart of included trials, presented in accordance with the PRISMA 2009 guidelines [32]. Twelve trials were included in the final qualitative synthesis and quantitative analysis. RCT = randomized controlled trial, OA = osteoarthritis, TKA = total knee arthroplasty.

Trial characteristics

Data were extracted for 616 patients scheduled for TKA due to knee OA (median (range), age 65.9 (62.1-70.7), BMI 31.0 (27.9-34.8), 58.6% female). Four of the 12 included trials were prospectively registered [29,43–45] while the remaining eight trials did not provide information on registration [28,35,46–51]. Five trials provided 'no pre-habilitation'/'care-as-usual' in the control group [29,46,49–51], three provided 'patient education/information' [44,45,48], three provided 'other lower extremities exercises' [28,35,43], and one trial provided 'exercises for the upper extremities' [47]. The pre-habilitation interventions included on average 1.8 knee-extensor exercises (range 1-3), an average duration of 6 weeks (range 4-8.9) and an average of 4.4 sessions/week (range 2-14), 2.5 knee-extensor sets/session (range 1.5-3.5) and 11 repetitions/set (range 8-15). Only two trials clearly reported the exercise intensity according to the 1 RM principle [28,29]. The pre-habilitation intervention for all trials were performed as supervised group sessions except one [35]. In four trials the supervised group sessions were supplemented with home-based exercise programs [43,49–51] (Table 1).

1

Table 1 – Characteristics of included trials

Author, year, trial design and registration	Patient characteristics (intervention group)	Patient characteristics (control group)	Pre-habilitation intervention (intervention group)	Pre-habilitation knee-extensor exercise dosage¥	Pre-habilitation intervention (control group)	Outcome measures†	End-points‡
Weidenhielm 1993 (49) RCT, not prospectively registered	n: 19 Age: 64 (4) BMI (kg/m^2): 30.1 % women: 57.9 Knee pain (no pain, mild pain, moderate pain, severe pain): 0, 1, 10, 8	n: 20 Age: 63 (5) BMI (kg/m^2): 29.1 % women: 45.0 Knee pain (no pain, mild pain, moderate pain, severe pain): 0, 2, 13, 5	Knee-extensor exercises: - Seated knee-extension with ankle weights Other exercises: - Warming up on bicycle - Knee mobility exercises - Strengthening exercises for the whole limb	Knee-extensor exercises: 1 Weeks: 5 Sessions/week: 7 (3 supervised session and the patients were recommended to practice the same program at home every day) Sets/session: 2 Repetitions/set: 10 Intensity/repetition (%RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 56.0	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 30°/s (Cybex II dynamometer)	Prior to TKA 3 months following TKA
Börjesson 1996 (51) RCT, not prospectively registered	n: 34 Age: 64 (4) BMI (kg/m^2): 28.4 % women: 50.0 Knee pain: Na	n: 34 Age: 64 (5) BMI (kg/m^2): 27.7 % women: 50.0 Knee pain: Na	Knee-extensor exercises: - Seated knee-extension with ankle weights Other exercises: - Knee mobility exercises - Strengthening exercises for the lower limb	Knee-extensor exercises: 1 Weeks: 5 Sessions/week: 5 (3 supervised and 2 at home) Sets/session: 2 Repetitions/set: 10 Intensity/repetition (%RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 40.0	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 30°/s (Cybex II dynamometer)	Prior to TKA

Beaurpre 2004 (46) RCT, not prospectively registered	n: 65 Age: 67 (7) BMI (kg/m^2): 32.0 (6.0) % women: 60.0 WOMAC pain: 49.0 (15.0)	n: 66 Age: 67 (6) BMI (kg/m^2): 31.0 (5.0) % women: 50.0 WOMAC pain: 49.0 (20.0)	Knee-extensor exercises: - Static quadriceps contraction - Short arc quadriceps contraction - Isotonic quadriceps contraction in sitting from 90° to zero degrees Other exercises: - Warmup: Hot pack applied to the involved knee - Low resistance cycling. - Hamstring contraction in sitting using tubing for resistance. - Straight leg raise to an approximate angle of 45° - Cool-down: Ice pack applied to the involved knee	Knee-extensor exercises: 3 Weeks: 4 Sessions/week: 3 Sets/session: 3 Repetitions/set: 12.5 (avg.) Intensity/repetition (%RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 86.4	No pre-habilitation provided	Knee-extensor strength: Isometric (hand-held dynamometer) PROM: WOMAC pain WOMAC stiffness WOMAC function	Prior to TKA 3 months following TKA
Rooks 2006 (48) RCT, not prospectively registered	n: 22 Age: 65 (8) BMI (kg/m^2): 35.7 (9.2) % women: 50.0 WOMAC pain: 7.0 (2.0)	n: 23 Age: 69 (8) BMI (kg/m^2): 33.9 (6.5) % women: 57.0 WOMAC pain: 6.5 (4.5)	Knee-extensor exercises: - Leg-press Other exercises: - Three weeks water-based exercise prior to land-based exercise - Seated row - Chest press	Knee-extensor exercises: 1 Weeks: 3 Sessions/week: 3 Sets/session: 2 Repetitions/set: 10 Intensity/repetition (%RM): Not reported. Estimated: 10 RM	Information from pre-operative education booklet	Knee-extensor strength: 1-repetition maximum leg-press PROM: WOMAC pain WOMAC function Function:	Prior to TKA

			- Biceps curls - Triceps kickback - Movements for the abdomen and shoulders - Flexibility exercises for hips, knees and ankles flexors and extensors and hip adductors	Knee-extensor exercise dosage: 14.4		Timed “Up & Go”	
Walls 2010 (35) Pilot RCT, not prospectively registered	n: 5 Age: 63.2 (11.4) BMI (kg/m^2): 32.8 (6.3) % women: 80.0 WOMAC pain: 10.0 (5.7)	n: 9 Age: 64.4 (8.0) BMI (kg/m^2): 30.7 (3.0) % women: 50.0 WOMAC pain: 11.7 (2.7)	Knee-extensor exercises: - Five second hold static quadriceps strengthening exercise in supine - Five second hold static quadriceps strengthening exercise in supine with cushion roll under the knee Other exercises: - Straight leg raises - Knee flexion and extensions exercises performed both sitting and, if tolerated, in standing	Knee-extensor exercises: 2 Weeks: 8 Sessions/week: 14 (twice daily) Sets/session: 1 (not reported Repetitions/set: 15 (avg.) Intensity/repetition (%RM): Not reported. Estimated: 15 RM Knee-extensor exercise dosage: 168.0	Isometric quadriceps strengthening exercise in sitting with toe against the wall (knee joint in 60° flexion) with neuromuscular electrical stimulation on the quadriceps muscle for 20 minutes a day on alternate days for the first two weeks and then every day for the next 6 weeks	Knee-extensor strength: Isometric (Biodex dynamometer) PROM: WOMAC pain WOMAC: stiffness WOMAC function Function: Stair climbing test	Prior to TKA 3 months following TKA

Swank 2011 (50) RCT, not prospectively registered	n: 36 Age: 63.1 (7.3) BMI (kg/m^2): 35.9 (8.5) % women: 66.7 Knee pain: Na	n: 35 Age: 62.2 (7.6) BMI (kg/m^2): 32.9 (5.7) % women: 62.9 Knee pain: Na	Knee-extensor exercises: - Squat - Seated knee-extension with elastic exercise bands Other exercises: - 5-minute warm-up consisting of light walking - Hip flexion - Hip extension - Hip abduction - Hip adduction - Ankle plantar flexion - Ankle dorsal flexion - Knee flexion - A series of forward and lateral step training exercises up and down a standard 8-inch step - Cool-down session of light static stretching followed by 5 minutes of light walking	Knee-extensor exercises: 2 Weeks: 5.5 (range 4-8) Sessions/week: 3 (1 supervised and 2 at home) Sets/session: 1.5 (avg.) Repetitions/set: 10 Intensity/repetition (%RM): Not reported. Estimated: 10 RM Knee-extensor exercise dosage: 39.6	No pre-habilitation provided	Knee-extensor strength: Isokinetically at 60°/s (Biodex 3 dynamometer) Function: Stair climbing test	Prior to TKA

McKay 2012 (47) Pilot RCT, not prospectively registered	n: 10 Age: 63.5 (4.9) BMI (kg/m^2): 35.0 (6.1) % women: 50.0 WOMAC pain: 10.1 (2.2)	n: 12 Age: 60.6 (8.1) BMI (kg/m^2): 33.8 (7.1) % women: 66.7 WOMAC pain: 11.9 (3.6)	Knee-extensor exercises: - Seated leg-press - Seated knee-extension Other exercises: - 10-minute aerobic warm-up (treadmill, cycling ergometer, rowing ergometer, or recumbent stepper) - Standing calf raise - Leg curl	Knee-extensor exercises: 2 Weeks: 6 Sessions/week: 3 Sets/session: 2 Repetitions/set: 8 Intensity/repetition (%RM): Not reported. Estimated: 8 RM Knee-extensor exercise dosage: 61.2	Placebo exercise program, upper body exercises: - 10-minute aerobic warm-up (treadmill, cycling ergometer, rowing ergometer, or recumbent stepper) - Seated latissimus dorsi [lat] pull, chest press, elbow flexion, elbow extension	Knee-extensor strength: Isometric at 75° knee flexion (leg-extension machine with a force meter attached to the lever arm) PROM: WOMAC pain WOMAC function Function: Stair climbing test 50-foot walk test	Prior to TKA 3 months following TKA
van Leeuwen 2014 (43) Pilot RCT, prospectively registered	n: 10 Age: 71.8 (7.5) BMI (kg/m^2): 27.9 (4.6) % women: 30.0 Knee pain: Na	n: 8 Age: 69.5 (7.1) BMI (kg/m^2): 27.9 (3.1) % women: 50.0 Knee pain: Na	Knee-extensor exercises: - Seated knee-extension (1-leg) - Seated leg-press (1 leg). - Squat Other exercises: - Step-up (1-leg) - Therapy included information and advice, exercise of activities of daily life, training of walking with aids, maintenance of mobility,	Knee-extensor exercises: 3 Weeks: 6 Sessions/week: 5 (2-3 supervised and 2-3 at home) Sets/session: 3.5 (avg.) Repetitions/set: 11 (avg.) Intensity/repetition (%RM): Not reported in RM. Estimated: 11 RM Knee-extensor exercise dosage: 252.0	Therapy included information and advice, exercise of activities of daily life, training of walking with aids, maintenance of mobility, and aerobic training (walking, cycling), but the patients in this group were not allowed to perform resistance training	Knee-extensor strength: Isometric at 75° knee flexion (custom-made dynamometer) Function: Stair climbing test Six-minute walk test	Prior to TKA 3 months following TKA

			and aerobic training (walking, cycling)				
Villadsen 2014 (44) RCT, prospectively registered	n: 41 Age: 67.1 (8.8) BMI (kg/m^2): 30.8 (4.9) % women: 61.0 KOOS pain: 47.8 (14.9)	n: 40 Age: 65.1 (9.0) BMI (kg/m^2): 33.4 (5.8) % women: 60.0 KOOS pain: 39.7 (12.6)	Knee-extensor exercises: - Seated knee-extension with elastic exercise bands Other exercises: - 10 min warm-up on ergometer cycle - Pelvic lift - Sit-ups - Slide-exercise forward-backward/forward lunge - Slide-exercise sideways/sideway lunge - Abduction with elastic exercise band - Adduction with elastic exercise band - Knee flexion with elastic exercise band - Chair stand - Step up and down a step-board - Cool-down - Basic education package (same as control group)	Knee-extensor exercises: 1 Weeks: 8 Sessions/week: 2 Sets/session: 2.5 (avg.) Repetitions/set: 12.5 (avg.) Intensity/repetition (%RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 32.0	Basic education package/care as usual (written information on the operating procedure, expected postoperative progress, and a leaflet on various exercises normally given when scheduled for total knee replacement)	Knee-extensor strength: Isometric at 75° knee flexion (custom-made dynamometer) PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: 20-meter walk test	Prior to TKA 3 months following TKA
Huber 2015 (45) RCT, prospectively registered	n: 22 Age: 68.8 (8.0) BMI (kg/m^2): 30.8 (4.9)	n: 23 Age: 71.9 (8.1) BMI (kg/m^2): 29.9 (5.5)	Knee-extensor exercises:	Knee-extensor exercises: 1 Weeks: 8.9 Sessions/week: 2	3 x Knee School: The knee school was taught by an	Knee-extensor strength: Isometric (hand-held pull gauge)	Prior to TKA 3 months following TKA

% women: 50.0 KOOS pain: 48.1 (17.6)	% women: 43.5 KOOS pain: 47.3 (16.8)	- Seated knee-extension with elastic exercise bands Other exercises: - Ergometer cycling for 10 minutes - Pelvic lift - Sit-ups - Slide-exercise forward-backward/forward lunge - Slide-exercise sideways/sideway lunge - Hip abductors/hip adductors with elastic band - Knee flexors with elastic band - Chair stands - Stair climbing - Mobility and stretching exercises - Cooling down (walking) - Knee School x 3	Sets/session: 2.5 (avg.) Repetitions/set: 12.5 (avg.) Intensity/repetition (%RM): Not reported. Estimated: 12.5 RM Knee-extensor exercise dosage: 35.6	experienced and specially-trained physiotherapist over 3 individual or group sessions, one session per week, starting about 4 weeks before the operation. Knee school sessions were separately organised for participants of the intervention group and those of the control group to avoid contamination. The content of the knee school included information on anatomy of the knee joint and adjacent functional structures, recommended activities with prosthesis and post-operative pain management, and details on the post-operative rehabilitation phase. Didactical elements included models of	PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: Timed "Up & Go" 20-meter walk test

					the knee joint and the lower extremity, working sheets, photos and videos, handouts, PowerPoint presentations and peer discussions		
Calatayud 2016 (28) RCT, not prospectively registered	n: 30 Age: 70.7 (7.3) BMI (kg/m^2): 32.0 (4.2) % women: Na WOMAC pain: 10.5 (0.9)	n: 29 Age: 70.1 (6.4) BMI (kg/m^2): 31.0 (3.8) % women: Na WOMAC pain: 10.6 (0.9)	Knee-extensor exercises: - Seated knee-extension - Seated leg-press Other exercises: - 15-min warm-up consisting of dynamic joint movements performed without ballistic movements and dynamic body weight exercises including 2 sets of 20 repetitions of step-ups and calf raises at a platform and finally 10 min of light-intensity hand or leg ergometry cycling (depending on the perceived pain) - A single warm-up set was also performed before each resistance training exercise by using a light resistance for 10 repetitions	Knee-extensor exercises: 2 Weeks: 8 Sessions/week: 3 Sets/session: 5 Repetitions/set: 10 Intensity/repetition (%RM): 10 RM Knee-extensor exercise dosage:192.0	Not reported in published paper. Information provided via e-mail correspondence with the corresponding author: "Before TKA, the control (usual care) did not receive any supervised intervention without any follow-up. Patients were just advised to perform three different isometric exercises everyday: (1) knee extension during 6–10 s while seated on a chair or table, 10–20 sets, 10–20 times/day; (2) hip flexion during 5–10	Knee-extensor strength: Isometric (hand-held dynamometer) PROM: WOMAC pain WOMAC: stiffness WOMAC function Function: Timed "Up & Go" Stair climbing test	Prior to TKA 3 months following TKA

			- Leg curl - Hip abduction - After completing the strengthening exercises, participants performed 4 sets of 30 s of double leg stance and 4 sets of 15 s of single leg stance on the same unstable device (Bosu) - 5-min cool-down of light static stretching of hip abductors, flexors and extensors of the knee and ankle plantar flexors		s while lying on mat with knee fully extended, 10–30 repetitions; (3) knee extension during 6–10 s while seated with legs extended horizontally on a mat, with a rolled towel under the knees, 10–20 sets, 10–20 times/day."		
Skoffer 2016 (29) RCT, prospectively registered	n: 30 Age: 70.7 (7.3) BMI (kg/m^2) median (range): 30.0 (22.6-42.5) % women: 63.3 KOOS pain: 53.0 (13.3)	n: 29 Age: 70.1 (6.4) BMI (kg/m^2) median (range): 31.8 (24.3-42.2) % women: 58.6 KOOS pain: 53.4 (13.5)	Knee-extensor exercises: - Seated knee-extension - Seated leg-press Other exercises: - 10-minute warm-up on a stationary bike - Knee flexio - Hip extension - Hip abduction - Hip adduction - 3x30 seconds of stretching of knee extensors, knee flexors and ankle flexors	Knee-extensor exercises: 2 Weeks: 4 Sessions/week: 3 Sets/session: 3 Repetitions/set: 10 Intensity/repetition (%RM): 10 RM Knee-extensor exercise dosage:57.6	No pre-habilitation provided	Knee-extensor strength: Isometric at 70° knee flexion (isokinetic dynamometer) PROM: KOOS pain KOOS adl function KOOS symptoms KOOS sport and recreation KOOS quality of life Function: Timed "Up & Go" Six-minute walk test	Prior to TKA 3 months following TKA

2

Table 1. Data is presented as mean (SD). RCT = randomized trial. BMI = Body mass index. KL = Kellgren-Lawrence scale. PROM = Patient reported outcome measure. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. KOOS = Knee osteoarthritis outcome score. Na = Not available. Pre-habilitation knee-extensor exercise dosage = (number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. When the exercise intensity was not provided the number of repetitions was used instead and the intensity is given as equivalent to this in % 1RM. ¥Exercises intensity estimated from number of repetitions and the Holten curve [42]. †Data extracted for present review. ‡End-points used for the present review.

Risk of bias within trials

None of the trials performed adequate blinding of patients and physiotherapists. “Selective outcome reporting” was assessed as unclear in eight of the trials as we could not locate a published trial protocol or registration. Three trials were assessed as high risk of bias as not all prespecified outcomes from the trial-registration were reported [29,43,45]. One trial was assessed as high risk bias under the domain “other sources of bias” as there was no reporting of the intervention in the control group [28] - information on this has later been provided via e-mail correspondence with the corresponding author (Table 1). Generally, the included trials lacked information on methods to reduce risk of bias and many were assessed as unclear (Figure 2).

	Weidenhielm 1993	Börjesson 1996	Beaupre 2004	Rooks 2006	Walls 2010	Swank 2011	McKay 2012	van Leeuwen 2014	Villadsen 2014b	Huber 2015	Calatayud 2016	Skoffer 2016
Sequence generation	?	?	?	?	+	?	?	+	?	+	+	?
Allocation concealment	?	?	?	?	?	?	?	-	+	+	+	?
Blinding of participants and personnel	?	?	?	?	?	?	?	-	?	?	?	-
Blinding of outcome assessor	?	?	?	?	+	?	?	+	+	+	?	+
Incomplete outcome data	+	+	+	-	+	+	+	-	+	+	+	-
Selective outcome reporting	?	?	?	?	?	?	?	-	+	-	?	-
Other sources of bias	?	?	?	?	?	?	?	?	+	+	-	+

Figure 2. Risk of bias within trials assessed with the Cochrane *Risk of Bias Tool* [38]. Each of the domains was evaluated as to whether they were adequate (green) (low risk of bias), unclear (yellow) or inadequate (red) (high risk of bias).

Dose-response

Meta-regression analysis showed no relationship between pre-habilitation knee-extensor exercise dosage and knee-extensor strength prior to (slope 0.0005 [95% CI -0.007 to 0.008]) (Figure 3) or at three months following TKA (slope 0.0014 [95% CI -0.006 to 0.009]). An inverse relationship was found between pre-habilitation knee-extensor exercise dosage and Timed "Up & Go" prior to TKA (slope -0.019 [95% CI -0.032 to -0.006]) but not three months following TKA. No relationship was found between knee-extensor dosage and knee pain, function, stair climbing test, short distance walk test and six-minute walk test neither prior to or three months following TKA (Supplementary material 1). The results were not altered when adjusting for co-variates age, BMI, knee-extensor strength at baseline and whether the control group received an active or passive intervention of the lower extremities. No adjustment was made for knee pain at baseline due to lack of observations.

Pre-operative effects of pre-habilitation

Twelve trials reported the effect of pre-habilitation on pre-operative knee-extensor strength [28,29,35,43–51]. Overall, a moderate effect favoring pre-habilitation for an increase in knee-extensor strength prior to TKA was found (SMD 0.50 [95% CI 0.12 to 0.88]), with substantial heterogeneity (I^2 = 78.5%) (Figure 4). For the secondary outcomes, pre-habilitation did not significantly improve knee pain, patient reported function, stair climbing test, Timed "Up & Go", short distance walking (15-25 m) or six-minute walk test prior to TKA (Figure 5). Large heterogeneity (I^2 >30%) was present in all meta-analyses and a random effects model was performed.

Post-operative effects of pre-habilitation

Nine trials reported the effect of pre-habilitation on three months post-operative knee-extensor strength [28,29,35,43–47,49]. Overall, we found no effect of pre-habilitation on knee-extensor strength three months following TKA (SMD -0.01 [95% CI -0.45 to 0.43]) (Supplementary material 2), with substantial heterogeneity (I^2 = 77.3%). No effect of pre-habilitation was seen in any post-operative outcomes (Figure 6).

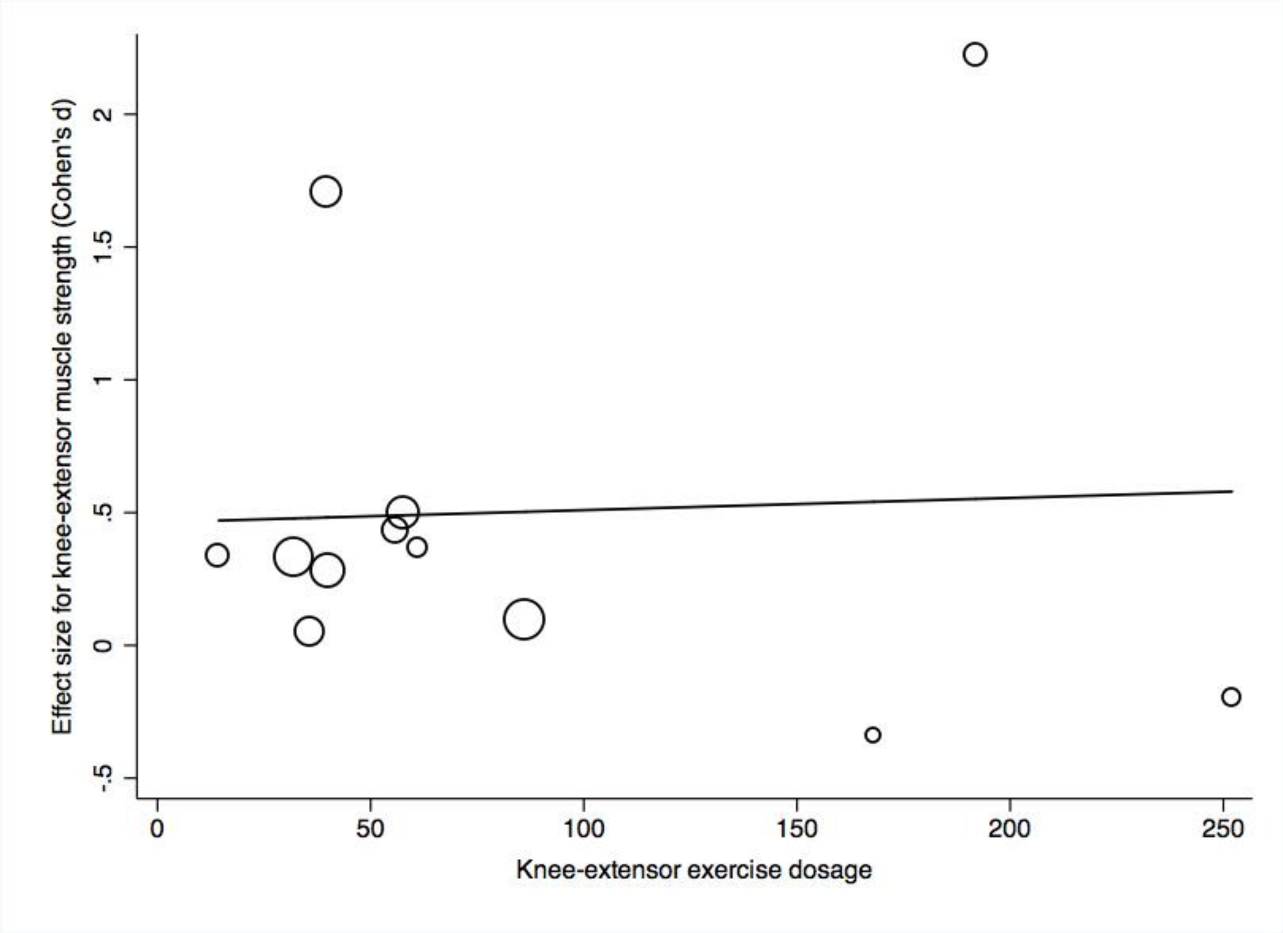

Figure 3. Unadjusted meta-regression analysis on the relationship of knee-extensor exercise dosage and pre-operative muscle strength. On the y-axis the effect size (SMD) of the dependent variable pre-operative knee-extensor strength is displayed. On the x-axis the independent variable is displayed, pre-habilitation knee-extensor exercise dosage:

(number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. The full black line shows the slope of the relationship between the knee-extensor exercise dosage and effect-size on muscle strength. The individual trials are shown by circles and the weight of the individual trials is shown by the size of the circles (i.e. larger circles indicate larger weight).

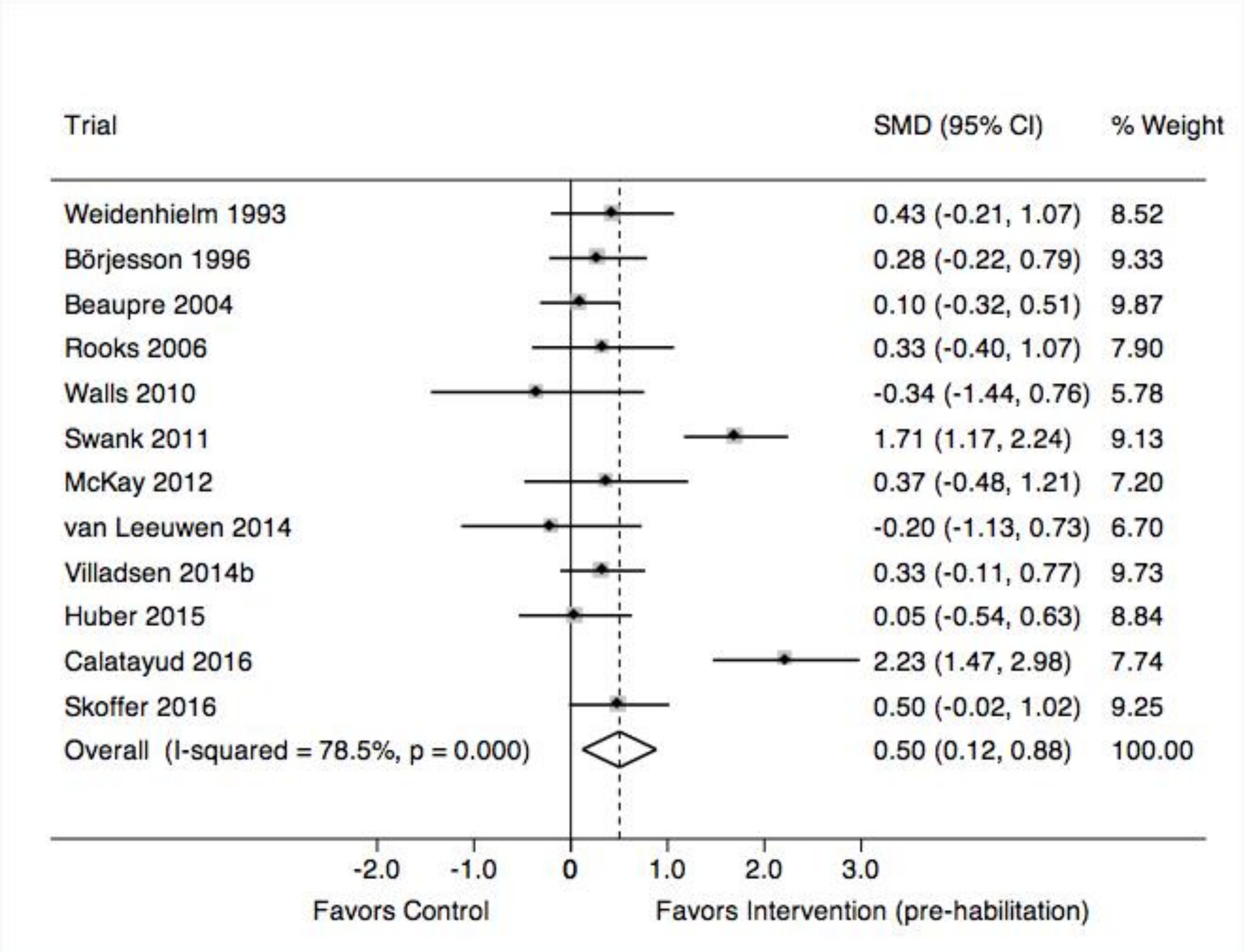

Figure 4. Forest plot of the effect of pre-habilitation including knee-extensor exercise on pre-operative knee-extensor muscle strength. SMD = standardized mean difference. Individual trial and total effect are shown with 95% confidence intervals ((SMD (95% CI)). Weights are from a random effect analysis.

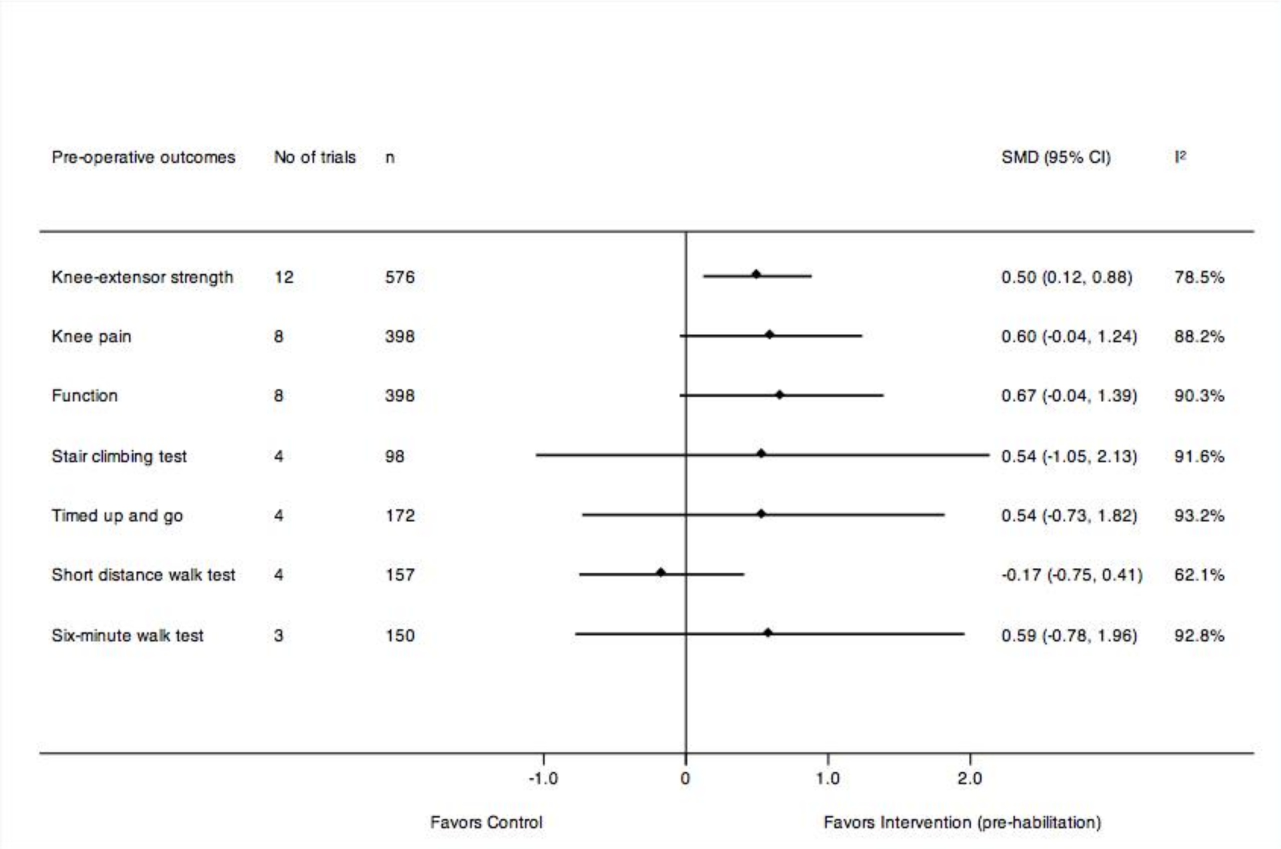

Figure 5. Forest plot of pooled effect sizes for all pre-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

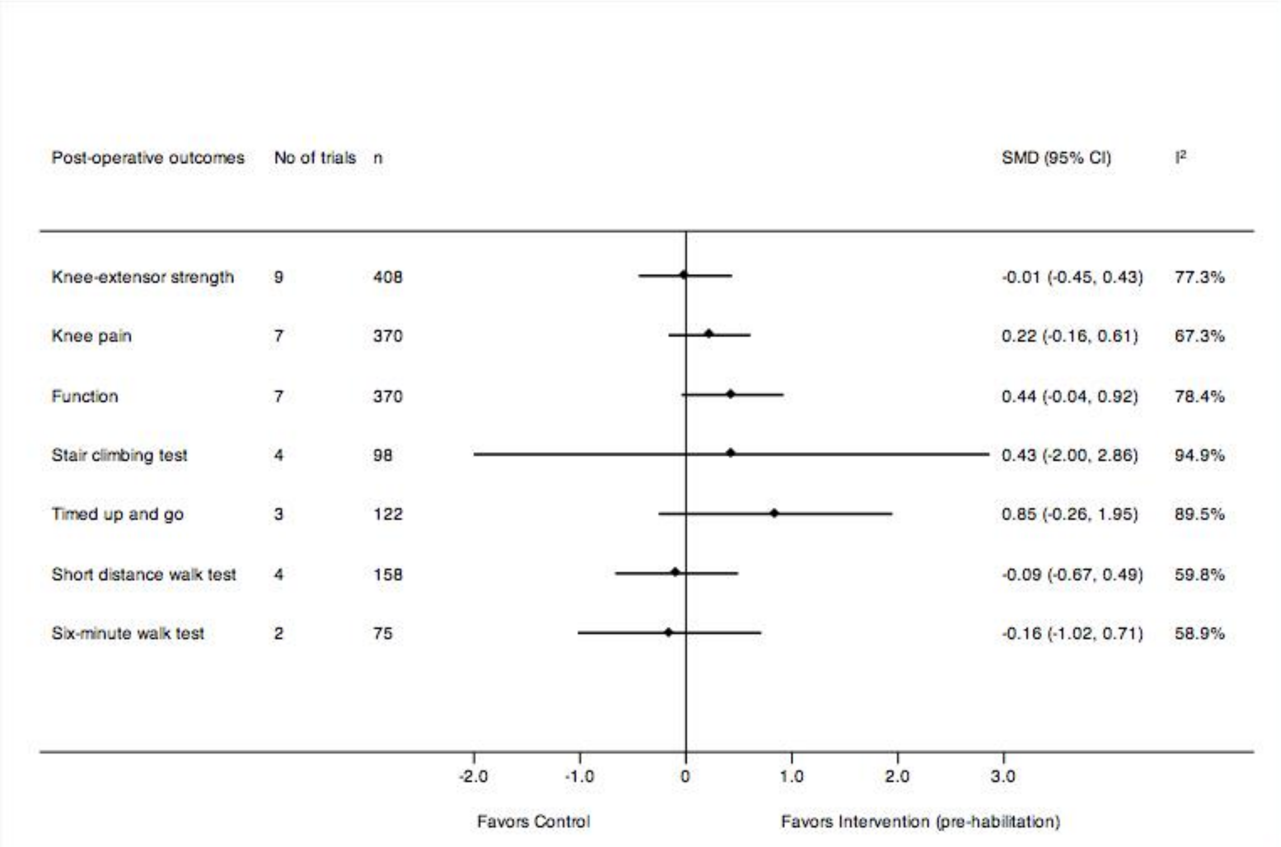

Figure 6. Forest plot of pooled effect sizes for all three months post-operative outcomes. SMD = Standardized mean difference. Total effects are shown with 95% confidence intervals ((SMD (95% CI)). I^2 = heterogeneity.

Risk of small study bias and exploring heterogeneity

The funnel plot did not show clear asymmetry and Eggers regression test showed no indication of small-study effects. The meta-analysis on pre-operative knee-extensor strength showed a between-study variance (Tau^2 = 0.3394). The between-study variance was reduced using meta-regression analysis adjusted for sex expressed as percentage women in individual trials (Tau^2 = 0.126) (slope 0.0540 [95% CI 0.016 – 0.0915]). Thus, with a 10% increase of women in the study, the SMD for knee-extensor muscle strength would increase by 0.5.

Discussion

This meta-analysis of 12 trials, including more than 600 patients, showed that pre-habilitation, including knee-extensor resistance training in patients eligible for TKA, was associated with a moderate increase in knee-extensor muscle strength prior to surgery but not three months following TKA. In the meta-regression analyses, no relationship was found between pre-operative knee-extensor exercise dosage and the effect on knee-extensor muscle strength neither prior to- or three months following TKA.

Pre-operative effects of pre-habilitation

When evaluating the effects of pre-habilitation prior to surgery in patients eligible for TKA, the importance of focusing on knee-extensor muscle strength is supported by the result of the present meta-analysis showing a moderate increase in knee-extensor muscle strength. Secondary outcomes, such as knee pain and function, were included to investigate whether changes in knee-extensor muscle strength were associated with more clinically relevant outcomes not as closely related to the exposure (knee-extensor resistance training). Knee pain and function changed in a positive direction favoring the intervention, though not statistically significant. This corresponds to the positive effects of exercise therapy reported in patients with mild-to-moderate knee OA [52]. The results suggest that a pre-operative increase in knee-extensor muscle strength might lead to slight pre-operative improvement in knee pain and function [53]. Pre-operative improvements in knee pain and function has previously been reported in patients eligible for TKA following exercise therapy [54]. The lack of significant effect on knee pain and function could be explained by insufficient increase in knee-extensor muscle strength. As an example, a 30-40% increase in knee-extensor strength has been suggested to improve knee pain and disability [55].

Post-operative effect of pre-habilitation

The effects of pre-habilitation prior to TKA were not seen three months following TKA and contradict the hypothesis that pre-operative changes also improve post-surgical outcomes. Thus, the potential of pre-habilitation to enhance post-operative rehabilitation does not seem likely, though there was a trend for improved function three months following TKA. A possible explanation for this, is that effects gained from pre-operative exercise is attenuated by the physiological stress induced by the surgical procedure of TKA , e.g. inhibiting neuromuscular function [6].

Legitimacy of pre-habilitation in patients eligible for TKA

The lack of effect of pre-habilitation following TKA questions the premise “Better in – better out” underlying the concept of “pre-habilitation” in TKA [8]. It seems more appropriate to refer patients eligible for TKA to rehabilitation with the purpose of improving knee OA related symptoms and not to “prepare” the patient for surgery, even though the patients fulfill the criteria for surgery. In line with this, a combined analysis of two trials showed that patients eligible for TKA experience clinical relevant changes following exercise therapy and 66% delay surgery for at least two years [54]. Another approach to “pre-habilitation” would be using it in shared decision-making when discussing the option of surgery [13]. As an example, a care pathway for a patient eligible for TKA could be outlined as follows: 1) assessment of symptoms and treatment options, 2) referral to exercise therapy and 3) re-assessment of symptoms and treatment options (e.g. surgery). A patient eligible for TKA who have had no improvement in knee related symptoms following exercise therapy could be scheduled for surgery, while a patient with improvements following exercise therapy could continue this treatment.

Dose-response

We found an inverse relationship between pre-habilitation knee-extensor exercise dosage and Timed “Up and Go” prior to TKA favoring a larger knee-extensor exercise dosage. Contrary to our hypothesis, we did not find a positive dose-response relationship for the other outcomes. A potential explanation for the general lack of positive dose-response relationships could be the assumptions that we had to make when calculating the exercise dosage. Assumptions about intensity was made as the exercise dosage descriptors were insufficiently reported in the included trials. We found it imperative to include the exercise intensity in the exercise dosage-calculation as the physiological response to resistance training is highly dependent on the intensity [56]. However, ten of the included twelve trials did not, or did not clearly, report the prescribed exercise intensity relative to 1RM. We requested this information from the corresponding authors during the data collection process. One author provided the information, three did not have it available and six did not reply to the request. As a consequence of this missing information and to refrain from subjective estimation of the exercise intensity based on information provided in the trials, we chose an approach of estimating the exercise intensity based on the number of repetitions by use of the Holten curve [42]. Though not optimal, we consider this the most objective and transparent approach to include exercise intensity in the dosage-calculation.

Generally, this challenge of inadequate intervention reporting is a well-recognized challenge in non-pharmacological interventions [57], not least in the reporting of exercise program details for patients with knee OA [58,59]. This creates challenges for many types of users of the published research, including clinicians, researches and patients. It may contributes to low clinical uptake, unnecessary research replication and “waste in research” and becomes a barrier for implementation [60,61]. More importantly is that clinicians and patients are not able to reproduce safe and effective interventions [59]. Together this calls for better reporting of exercise characteristics by using templates such as the TIDieR (Template for Intervention Description and Replication) [62] and CERT checklists [36] and the mechanobiological exercise descriptors outlined by Toigo and Boutellier [37]. Further, only four of the included twelve trials had a pre-registered and public available trial protocol summary, and none had a public available full trial protocol (e.g. published trial protocol). The processes of trial pre-registration and protocol publication could contribute to more detailed description of exercise interventions as trial protocol guidelines would refer to the above mentioned templates for reporting exercise characteristics [63,64].

Another potential explanation for the lack of a positive dose-response relationship is that patients eligible for TKA can achieve an increase in their knee-extensor muscle strength by exercising at lower intensities. This would be supported by the result from the present meta-regression analysis. Patients eligible for TKA are not very physically active due to limitations related to their knee condition [65,66]. Inactive lifestyle leads to decrease in muscle strength and physical ability, especially in older adults [67–69] leaving a large potential for improvement [56]. Potentially, patients eligible for TKA do not need to exercise with high intensity to achieve muscle strength improvements [70]. As an example, in untrained healthy individuals loads of 45-50% of 1 RM have been shown to increase muscle strength [56]. However, the forest-plot of the effect of pre-habilitation prior to TKA on knee-extensor strength (Figure 4) also show that not all trials found an effect on knee-extensor strength.

Future research should focus on pre-registered, randomized dose-response trials in patients potentially eligible for TKA with clear exercise reporting and assessment of adherence [71–73].

Strengths and limitations

This is the first dose-response analysis on pre-habilitation in patients eligible for TKA to account for several exercise dosage descriptors including exercise intensity. Unfortunately, sufficient information was not available to calculate a credible exercise dosage and the approach we used to estimate exercise intensity could have introduced bias. A limitation of this review is that we did not analyzed on adherence to the prescribed exercise interventions. We analyzed the prescribed exercise dosage but no data on the actual performed exercise dosage was provided, excluding the option of adjusting for exercise adherence. As an example, in an exercise program prescribing 15 repetitions per set but not providing the exercise intensity there is a risk that the patient performed the exercise with a suboptimal intensity. Thus, the intensity used in the dosage-calculation is based on the premise that all patients exercised with an intensity corresponding to the repetitions performed in each set. Further, in eleven of the included twelve trials the exercise interventions were described as supervised, however no data was provided on how much control there was on completion of the prescribed exercise dosage.

Conclusions

We found no relationship between pre-operative knee-extensor exercise dosage and change in knee-extensor strength. Pre-operative exercise including knee-extensor muscle strength exercise increased knee-extensor strength moderately prior to but not three months following TKA.

Author contribution

Conception and design: Husted, Juhl, Rathleff and Bandholm.

Data acquisition: Husted, Rathleff and Bandholm.

Analysis and interpretation of the data: All authors.

Drafting of the article: Husted.

Critical revision of the article for important intellectual content: All authors.

Statistical expertise: Juhl.

Final approval of the article: All authors. Mr. Husted (rasmus.skov.husted@regionh.dk) and Prof. Bandholm (thomas.quaade.bandholm@regionh.dk) takes responsibility for the integrity of the work as a whole.

Competing interests statement

None of the authors have competing interests in relation to this work.

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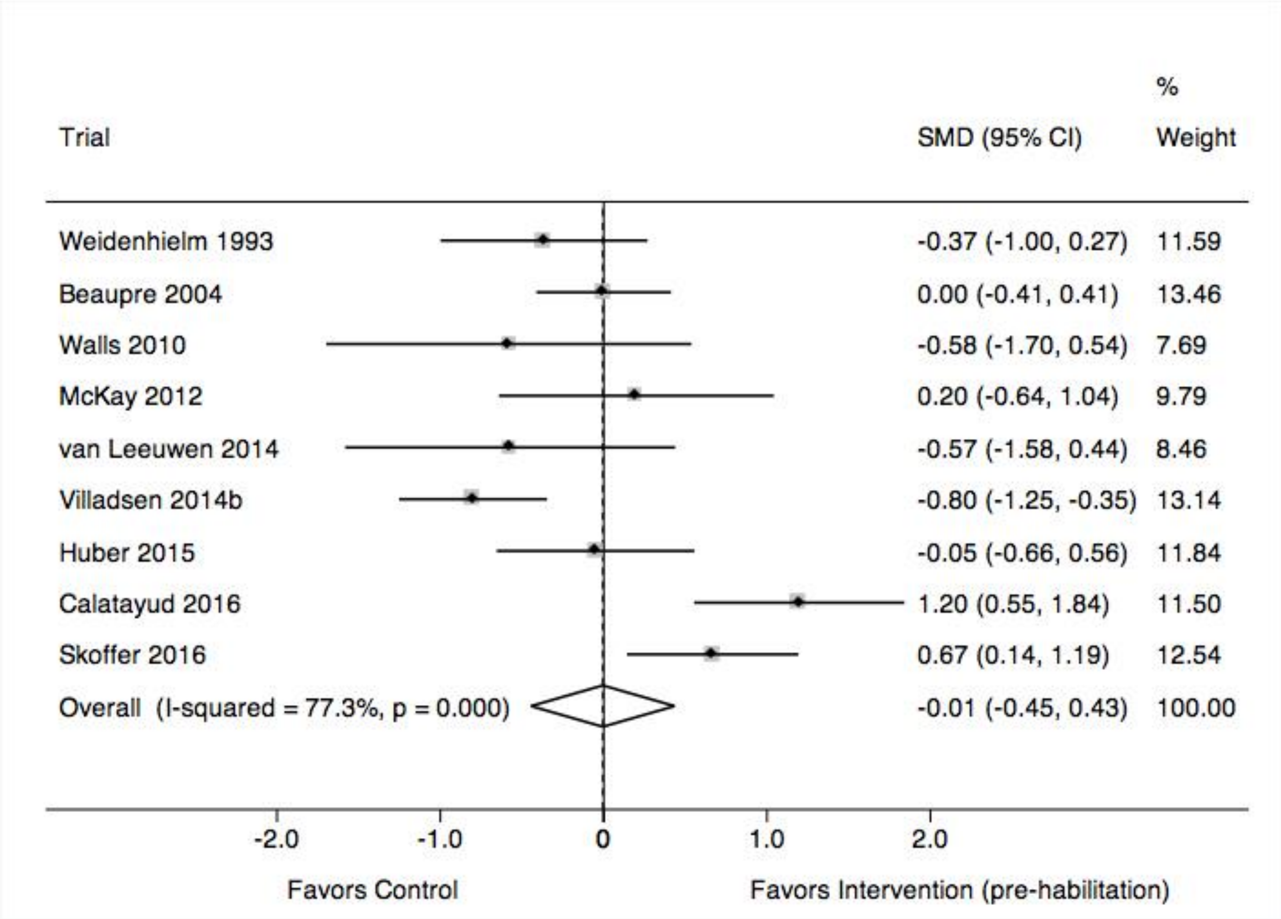
Supplementary material 1.

Independent variable	Dependent variable	Slope	95% CI
	Prior to TKA		
Pre-habilitation knee-extensor exercise dosage	Knee-extensor strength	0.0005	-0.007 to 0.008
	Knee pain	-0.012	-0.028 to 0.004
	Patient reported function	0.016	-0.005 to 0.038
	Stair climbing test	-0.005	-0.063 to 0.052
	Timed "Up & Go"	-0.019	-0.032 to -0.006
	Short distance walk test	0.012	-0.007 to 0.031
	Six-minute walk test	-0.006	-0.101 to 0.088
	Three months following TKA		
	Knee-extensor strength	0.0014	0.006 to 0.009
	Knee pain	-0.003	-0.12 to 0.006
	Patient reported function	0.004	-0.006 to 0.016
	Stair climbing test	-0.0.13	-0.365 to 0.338
	Timed "Up & Go"	-0.012	-0.050 to 0.024
	Short distance walk test	0.012	-0.007 to 0.031
	Six-minute walk test	N.A.	N.A.

Supplementary material 1. Pre-habilitation knee-extensor exercise dosage = (number of knee-extensor exercises*weeks*sessions/week*sets/sessions*repetitions/set)*exercise intensity/repetitions per set. N.A. = too few observations for analysis.

Supplementary material 2.



Supplementary material 2. Forest plot of the effect of pre-habilitation including knee-extensor exercise on three months post-operative knee-extensor muscle strength. SMD = standardized mean difference. Individual trials and total effects are shown with 95% confidence intervals ((SMD (95% CI)). Weights are from a random effect analysis.

Paper II

Efficacy of pre-operative quadriceps strength training on knee-extensor strength before and shortly following total knee arthroplasty: protocol for a randomized, dose-response trial (The QUADX-1 trial)

Rasmus Skov Husted, Anders Troelsen, Kristian Thorborg, Michael Skovdal Rathleff, Henrik Husted and Thomas Bandholm

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Trials

STUDY PROTOCOL Open Access

Efficacy of pre-operative quadriceps strength training on knee-extensor strength before and shortly following total knee arthroplasty: protocol for a randomized, dose-response trial (The QUADX-1 trial)

Rasmus Skov Husted[1,2,3,4*], Anders Troelsen[4], Kristian Thorborg[1,2,5], Michael Skovdal Rathleff[6,7], Henrik Husted[4] and Thomas Bandholm[1,2,3]

Abstract

Background: Patients with knee osteoarthritis (OA) report knee pain, limitation in physical activities and low quality of life. The two primary treatments for knee OA are non-surgical treatment (e.g., exercise) and surgery (total knee arthroplasty (TKA)); however, national guidelines recommend non-surgical treatment to be tried prior to surgical procedures. Patients with knee OA are characterized by decreased muscle strength, particularly in the knee-extensor muscles. Correspondingly, decreased knee-extensor strength is found to be associated with an increased risk of development, progression and severity of knee OA symptoms. Recent trials suggest a positive effect of pre-operative exercise on pre- and post-operative outcome; however, the most effective pre-operative knee-extensor strength exercise dosage is not known. The purpose of the present trial is to investigate the efficacy of three different exercise dosages of pre-operative, home-based, knee-extensor strength exercise on knee-extensor strength before and shortly after surgery in patients eligible for TKA due to end-stage knee OA.

Methods: In this randomized dose-response trial with a three-arm parallel design, 140 patients with end-stage knee OA (candidates for TKA) are randomized to one of three exercise dosages (two, four or six session/week) of knee-extensor strength exercise (three sets, 12 repetitions at 12 RM, per exercise session) for 12 weeks. The knee-extensor strength exercise is home-based (unsupervised) and performed with an elastic exercise band following an initial exercise instruction. Adherence is objectively quantified using a sensor attached to the exercise band. The primary outcome will be the change in knee-extensor strength. Following the 12-week exercise period, the need for TKA surgery is re-assessed by an orthopedic surgeon.

Discussion: Decreased knee-extensor strength is a major challenge in patients with knee OA. Exercise programs focusing on knee-extensor strength are found to be more effective in relieving knee OA pain and symptoms compared to more general exercise programs. However, the optimal exercise dosage for knee-extensor strength deficits in patients with knee OA is inconclusive. Knowledge on the dose-response relationship for knee-extensor strength exercise in patients with knee OA will help guide future non-surgical treatment in this patient population.
(Continued on next page)

* Correspondence: rasmus.skov.husted@regionh.dk
[1]Physical Medicine and Rehabilitation Research - Copenhagen (PMR-C), Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[2]Department of Physical and Occupational Therapy, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
Full list of author information is available at the end of the article

(Continued from previous page)

Trial registration: ClinicalTrials.gov, ID: NCT02931058. Pre-registered on 10 October 2016.

Keywords: Knee osteoarthritis, Knee-extensor exercise, Exercise therapy, Strength training, Dose-response, Total knee arthroplasty

Background

Patients diagnosed with knee osteoarthritis (OA) report pain, low quality of life and limitation in physical activities [1]. As a consequence, in Denmark, around 8000 patients with end-stage knee OA receive surgical treatment annually, in the form of total knee arthroplasty (TKA), to overcome their knee-related disabilities [2]. Currently, the two primary treatments for knee OA are non-surgical treatment (e.g., pain treatment, exercise and weight loss if indicated) and surgery (TKA) [3].

There is preliminary evidence that pre-operative exercise may postpone total hip arthroplasty in patients with hip OA [4]. Likewise, pre-operative exercise in candidates for TKA will provide an optimized basis for deciding whether to commence TKA; e.g., patients experiencing pain relief and functional improvement following exercise might benefit from postponing their potential TKA and vice versa. The latest systematic review on the efficacy of pre-operative strength exercise to enhance post-operative recovery after TKA and THA concludes that pre-habilitation may slightly improve early post-operative pain and function among patients undergoing total joint replacement; but the effects are too small and short-lived to be considered clinically important [5]. However, this conclusion is based on trials with significant limitations, providing very low certainty in estimates [5].

Recently, the first randomized controlled trial investigating the efficacy of TKA in patients eligible for TKA was conducted [6]. It showed an added effect (pain relief and functional improvement) of 30% by TKA and non-surgical treatment to that achieved by non-surgical treatment alone (30%). This highlights the importance of coordinating non-surgical and surgical care to select the right candidates for surgery, especially as patients undergoing TKA seem to experience more serious adverse events compared to non-surgical treatment [6]. These results suggest that non-surgical treatment should at least be tried out and considered before commencing surgical procedures. Optimally, patients awaiting TKA would conduct home-based, pre-operative exercise as the effect of exercise helps to establish the potential need for a future orthopedic operation. At the same time, it would be a potential solution of little cost and it enables the patients to self-manage their symptoms.

Patients with knee OA are characterized by decreased knee-extensor strength and this decrease in knee-extensor strength is associated with limitation of activities of daily living, independent of knee pain [7, 8]. Correspondingly, knee-extensor muscle weakness is found to be associated with increased risk of developing knee OA, progression of knee OA, symptoms of knee pain and decline in function [9, 10]. Clinically, patients diagnosed with end-stage knee OA who are awaiting TKA to reduce pain and disability are reported to have 35% reduced knee-extensor strength compared to healthy, age-matched persons [7]. Shortly after TKA, patients lose an additional 80% of their pre-operative knee-extensor strength [11]. This massive loss in knee-extensor strength severely limits functional performance and may delay hospital discharge in the large number of patients undergoing TKA every year [12]. One of the latest systematic reviews on the efficacy of exercise to reduce pain and disability in patients with knee OA showed that isolated knee-extensor strength exercise was more effective in reducing pain and disability if not combined with other forms of exercises (e.g., other muscle groups or cardiovascular training) [13]. In line with this, the 2014 international guidelines for non-surgical management of knee OA include strength exercise of the knee-extensor muscles [14].

Two recent randomized controlled trials have indicated that high-volume, pre-operative strength exercise may enhance pre- and post-operative knee-extensor strength as well as functional performance in patients undergoing TKA [15, 16]. Hence, there are indications that the applied pre-operative exercise dose seems related to pre- and post-operative efficacy, making a dose-response trial of pre-operative exercise particularly relevant.

Purpose

The purpose of the present trial is to investigate the efficacy of three different exercise dosages (two, four and six exercise sessions per week) of pre-operative, home-based, knee-extensor strength exercise on knee-extensor strength before and shortly after surgery in patients eligible for TKA due to end-stage knee OA.

Hypothesis

We hypothesize that a dosage of four knee-extensor strength exercise sessions per week will elicit the greatest strength increase pre-operatively compared to two or six sessions per week. The recommended minimum exercise dosage required for strength gains according the American College of Sports Medicine is two sessions per week [17]; therefore, two greater dosages are investigated and used as comparators. Four sessions per week is likely optimal and six sessions per week probably have no additional benefit, but could potentially increase knee pain [18, 19].

Methods

Literature search and search matrix

Before commencing the planning of this trial, a systematic literature search was conducted to locate trials investigating the same research question or planning to do so (protocols). The following search matrix (developed using a PICOT approach [20]) was used to search MedLine through pubmed.com on 18 November 2015 with weekly updated searches:

((((((((((("end stage osteoarthritis") *or* (("Osteoarthritis"[Mesh]) *or* "Osteoarthritis, Knee"[Mesh])) *or* osteoarthritis)))) *or* "knee osteoarthritis"[Title/Abstract])) *and* ((((((((("resistance training"[Title/Abstract]) *or* "Resistance Training"[Mesh]) *or* "strength training"[-Title/Abstract]) *or* physiotherapy[Title/Abstract]) *or* "Physical Therapy Specialty"[Mesh]) *or* "Physical Therapy Modalities"[Mesh]) *or* "knee extensor training"[Title/Abstract]) *or* "quadriceps training"[Title/Abstract]) *or* "pre-operative training"[Title/Abstract]) *or* "physical function"[-Title/Abstract])) *and* (((((("pre-operative strength"[Title/Abstract]) *or* "knee extensor strength"[Title/Abstract]) *or* "quadriceps strength"[Title/Abstract]) *or* "Pain"[Mesh]) *or* pain[Title/Abstract]) *or* "Musculoskeletal Pain"[Mesh])) *and* ((((((("post-operative strength"[Title/Abstract]) *or* "post-operative knee extensor strength"[Title/Abstract]) *or* "knee extensor strength"[Title/Abstract]) *or* "quadriceps strength"[Title/Abstract]) *or* "Pain"[Mesh]) *or* pain[Title/Abstract]) *or* "Musculoskeletal Pain"[Mesh]) *and* (((((((meta-analysis[Title/Abstract]) *or* "Meta-Analysis"[Publication Type]) *or* "systematic review"[Title/Abstract]) *or* "Review"[Publication Type]) *or* "randomized controlled trial"[Title/Abstract]) *or* "Randomized Controlled Trial"[Publication Type]) *or* "prospective cohort"[Title/Abstract]).

Systematic reviews and meta-analyses were found but none specifically addressed the pre-operative effect on muscle strength of a single knee-extensor strength exercise in patients with knee OA. No Cochrane reviews were found. An updated search was performed on 1 May 2017 providing new academic literature relevant for the scope of this trial [21, 22].

Trial design

The trial is named the *QUADX-1 trial*. It uses a three-arm, parallel-group, randomized trial design with three intervention groups (exercise dosages) and no control group. No control group is included as the primary purpose of the trial is to investigate the dose-response relationship of the investigated knee-extensor strength exercise dosages. Based on the sample size estimation outlined below, 140 patients will be randomized (1:1:1) to one of three exercise dosages for 12 weeks. Outcomes will be assessed blinded at baseline before the start of the exercise (t_0), after the exercise intervention, which is before possible surgery (t_1, primary endpoint), at hospital discharge 1–8 days after surgery (if performed) (t_2) and, finally, at 3 months after surgery (if performed) (t_3). A flow chart of the trial is provided below (Fig. 1).

This clinical trial protocol is based on the PREPARE trial guide [23] and the SPIRIT Checklist (Fig. 2, Additional file 1) [24]. The trial report will adhere to the Consolidated Standards of Reporting Trials (CONSORT) Checklist using the extension for non-pharmacological treatments [25]. The TIDieR Checklist will be used for intervention description (Additional file 2) [26]. The trial was pre-registered at ClinicalTrials.gov on 10 October 2016 (ID: NCT02931058, https://clinicaltrials.gov/ct2/show/NCT02931058) and approvals with the Ethics Committee of the Capital Region Denmark (ID: H-16025136) and the Danish Data Protection Agency (J. nr.: 2012-58-0004. Lokale RegH j. nr.: AHH-2016-072, med I-Suite nr.: 04980) were obtained before the first patient was enrolled. The trial will be conducted at Copenhagen University Hospital Hvidovre and in the collaborating municipalities of Copenhagen, Hvidovre and Brøndby, Denmark.

Recruitment

All patients will be included by consecutive sampling from the orthopedic outpatient clinic at Copenhagen University Hospital, Hvidovre. At the orthopedic outpatient clinic, possible patients for TKA surgery due to end-stage knee OA are introduced to the trial and offered to participate by the orthopedic surgeon if they fit the initial eligibility criteria (please see below). On the same day, eligible patients interested in participating in the trial are then referred to a research assistant who provides thorough oral and written information about the trial. Eligible patients are informed that participation in the project includes 12 weeks of home-based, knee-extensor strength exercise with the purpose of improving knee-extensor strength, relieving knee pain and improving functional performance. Further, they are informed that after the exercise period, they will be re-assessed at the orthopedic outpatient clinic with regards to undergo surgery or not. To prevent performance bias, eligible patients are blinded to the exercise dosage randomization as well as the trial hypothesis. Information about the trial is provided in a calm setting dedicated to the trial. Should the patients wish for a companion to be present during the information meeting a new information appointment is scheduled. Along with the information, a second more thorough screening of inclusion and exclusion criteria is

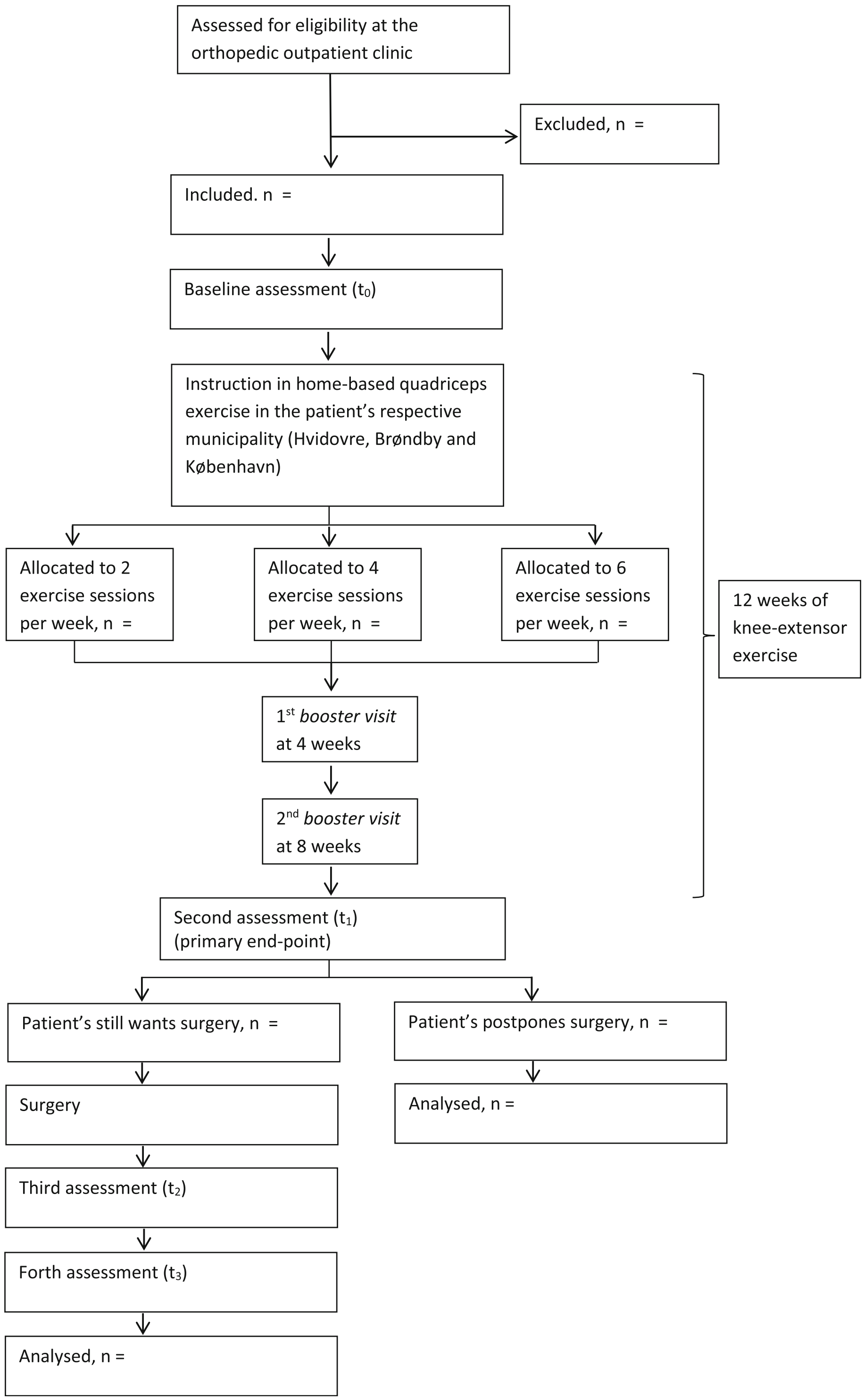

Fig. 1 Flow chart of enrollment, randomization, treatment and follow-up

commenced. The patients are given a minimum of 24 h to decide whether they would like to participate in the trial or not. If the patients decide to participate, a baseline assessment is scheduled. Written informed consent is obtained at the baseline assessment. Once written informed consent and baseline assessment is completed, the patient is fully included in the trial. Outcome assessments will be performed blinded by the primary

Table 3 Schedule for enrolment, intervention and outcome assessments

	Pre-allocation	Allocation	Post-allocation		
	$-t_0$	t_0	t_1	t_2	t_3
	Enrolment	Week 0	After 12 weeks exercise (primary end-point)	After surgery at hospital discharge	Three months after surgery
ENROLMENT:					
Eligibility screening	X				
Informed consent	X				
Patient characteristics		X			
Allocation		X			
INTERVENTIONS:					
Intervention					
Group 2) 2 sessions/week		X			
Group 4) 4 sessions/week		X			
Group 6) 6 sessions/week		X			
Control group		na			
ASSESSMENTS:					
Muscle strength and functional measurements					
- Isometric knee-extensor strength (primary outcome)		◆———	————	———◆	
- 6 min walk test for distance (6MWT)		◆———	————	———◆	
- Stair climb test (SCT)		◆———	————	———◆	
Patient Reported Outcome Measures (PROMs)					
- Knee Osteoarthritis Outcome Score questionnaire (KOOS)		X	X		X
- Oxford Knee Score (OKS)		X	X		X
Other outcomes					
- Current knee pain (Numeric Rating Scale, NRS)		◆———	————	———◆	
- Knee pain during the last week (Numeric Rating Scale, NRS)		X	X		X
- Need for surgery			X		
- Exercise adherence (sessions) and volume (sets, reps, time under tension)			X	X	
- Adverse events		◆———	————	———◆	

Fig. 2 Schedule for enrollment, intervention and outcome assessments (Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT))

investigator and a research assistant dedicated to the trial, who are both trained according to the trial outcome-assessment protocol to ensure standardized assessments throughout the trial. To further refine and ensure standardization of the trial outcome-assessment protocol we piloted the outcome-assessment procedures in seven patients prior to initiating the trial.

Eligible criteria

Inclusion criteria

- Patient is a possible candidate for a primary TKA due to knee OA, based on the below terms:
    - Knee pain ≥ 3 (Numeric Rating Scale) in the last week
    - Kellgren-Lawrence classification grade ≥ 2
- Patient is eligible for home-based, knee-extensor strength exercise
- Patient is age ≥ 45 years
- Patient is resident in one of the three municipalities (København, Hvidovre or Brøndby) involved in the trial
- Patient is able to speak and understand Danish

Exclusion criteria

- Exercise is contra-indicated for the patient
- Patient has a neurological disorder
- Patient has a diagnosed systemic disease (American Society of Anesthesiologists' physical status classification score (ASA) ≥ 4)
- Patient with terminal illness
- Patient has severe bone deformity demanding use of non-standard implants
- Weekly alcohol consumption above national recommendations (>7 units for women, > 14 units for men)

Protocol amendments

- 8 February 2017: Inclusion criteria *age* changed from ≥ *50 years* to ≥ *45 years*. The rationale for this modification is that patients aged 45–49 years with knee OA who are possible candidates for TKA are likely to benefit from participation. Recent comparable trials of pre-operative exercise on the same population had age-related inclusion criteria including the age-span of 45–49 years of age [27, 28]
- 8 February 2017: Exclusion criteria *ASA score* changed from ≥ *3* to ≥ *4*. The rationale for changing the exclusion criteria relating to the ASA score is that patients with knee OA and an ASA score of 3 who are possible candidates for TKA are likely to benefit from participating in the trial. An ASA score of 3 is defined as "*A patient with severe systemic disease*," while an ASA score of 4 is defined as "*A patient with severe systemic disease that is a constant threat to life*" [29]. One definition-difference between ASA score 3 and 4 is the functional capacity, where a patient with an ASA score of 3 is able to complete a flight of stairs or walk 200 m on level ground, whereas a patient with an ASA score of 4 is not able to do this [29]. Thus, patients with knee OA and an ASA score of 3 who are possible candidates for TKA are able to participate in the present exercise trial
- 30 March 2017: Inclusion criteria *knee pain (Numeric Rating Scale (NRS)) in the last week* changed from > *3* to ≥ *3*. The rational for changing the NRS from > 3 to ≥ 3 is that some patients who are considered candidates for total knee replacement might not have pain scores higher than 3. Thus, they might end up being excluded from the trial even though they are clinically considered candidates for total knee replacement. Hence, this change was made to reflect current clinical practice
- 30 March 2017: Inclusion criteria *Oxford Knee Score* (OKS) was removed as an inclusion criterion but still kept as a descriptive and effect outcome. The rationale for this modification (removing OKS as an inclusion criteria) is that OKS is not used in daily clinic practice as a means of assessing whether a patient is a candidate for TKA or not. Thus, keeping the OKS as an inclusion criterion in the QUADX-1 trial will not reflect current clinical practice
- All the above protocol amendments are approved by the Ethics Committee of the Capitol Region Denmark (ID: H-16025136; 55528, 55529, 57312)

Intervention

Once the baseline assessment is completed, the patients are referred to their local municipality rehabilitation setting for knee-extensor strength exercise instruction. The initial exercise instruction takes place there, where the patients are received by a trial-dedicated physiotherapist who is specialized in instructing and training patients with knee OA. Once the instruction is completed and the patients are comfortable with the exercise, an exercise session is completed under supervision from the physiotherapist. The patients are handed personal elastic exercise bands for exercise at home and a study-specific brochure where instruction notes to the exercise are illustrated and described (Additional file 3). All the physiotherapists dedicated to the trial were trained by the primary investigator prior to the start of the trial to ensure standardized exercise instruction and information across the physiotherapists.

The intervention period is 12 weeks. After 4 and 8 weeks of exercise, the patients have an exercise quality check-up (booster visit) with the physiotherapist in the municipality setting. The exercise quality check-up includes exercise technique re-assessment (fractional and temporal distribution of the contraction modes, range of motion and positioning), ensuring optimal length or type of elastic exercise band (resistance corresponding to 12 repetitions-maximum (RM)) and exercise-related questions from the patients.

Three exercise dosages are investigated; two, four and six sessions per week for 12 weeks (group 2, 4 and 6, respectively) (Table 1). Each exercise session comprises a single-strength training exercise, knee-extension, which is performed in three sets with 12 repetitions at a load corresponding to 12 RM in each set. There is no control group. The patients are randomly allocated to one of the three exercise dosages. The patients are instructed to perform only one exercise session per day. That is, they are not allowed to combine several exercise sessions on the same day. For example, patients randomized to group 6 are instructed to exercise 6 days of the week.

The intervention is personalized to the extent where each patient is exercising with an individual absolute resistance in the elastic exercise band corresponding to a relative load of 12 RM. Contractions should be continued until volitional muscular failure. That is, until the knee-extensor muscles are maximally fatigued and the patient is not able to perform further repetitions. If volitional muscular failure occurs before 12 RM, the resistance of the elastic band is adjusted so that the pre-determined number of repetitions can be completed. Whenever a given resistance in the elastic exercise band becomes too low (i.e., more than 12 repetitions per set can be performed), the patients are instructed to adjust the resistance in the elastic exercise band (increase the distance between the two endpoints of the elastic exercise band, i.e., moving the chair further away from the door (Fig. 3)) to achieve a new resistance corresponding to a relative load of 12 RM. The home-based, knee-extensor strength exercise

Table 1 Exercise sessions per week according to exercise dosage randomization

Dosage groups	Sessions/week					
Gp. 2 – 2 sessions/week	3*12 RM			3*12 RM		
Gp. 4 – 4 sessions/week	3*12 RM	3*12 RM		3*12 RM	3*12 RM	
Gp. 6 – 6 sessions/week	3*12 RM	3*12 RM	3*12 RM	3*12 RM	3*12 RM	3*12 RM

Knee-extensor exercise dosages investigated

(Fig. 3 and Fig. 9, Supplementary online video [30]) is described in detail below (Table 2) according to the mechanobiological descriptors from Toigo and Boutellier [31].

Criteria for modifying and discontinuing

Criteria for discontinuing

Patients are instructed to stop exercising if they experience a *strong flare up* or a *strong aggravation* of knee-related symptoms (e.g., pain and swelling), i.e., knee-related symptoms that are intolerable for the patient. Correspondingly, patients are encouraged to complete the exercise if they experience minor and moderate knee-related symptoms [32]. Should the patients experience intolerable symptoms (stopping with exercise); they are provided with a telephone number to a physiotherapist (the trial manager) and are encouraged to call. The trial manager fills out a standardized form at these calls.

Criteria for modifying

Should the patients experience strong knee-related symptoms, they are instructed to lessen the resistance in the elastic exercise band (shortening the distance between the endpoints of the elastic exercise band, i.e., moving the chair closer to the door (Fig. 3)). Importantly though is that this reduced resistance in the elastic exercise band does not comprise the exercise resistance corresponding to 12 RM, (i.e., too little resistance in the elastic exercise band). This is explained to the patients at the exercise instruction session and mentioned in the brochure handed to the patients along with the elastic exercise band (Additional file 3).

Participant compliance, retention and concomitant care

At the baseline outcome assessment and at the exercise instruction session the patients are encouraged to complete the full intervention and the patients are handed an information brochure about both how to conduct the exercise, with encouragement to complete the intervention and with information on how to handle kinesiophobia (Additional file 3). Further, the patients have two exercise quality check-up visits (booster visits): one at 4 weeks and one at 8 weeks, with the physiotherapist in the municipality setting. These booster visits also serve as promoters for exercise adherence. The patients should continue their lives without changing any concomitant care or interventions, except extra exercise of the quadriceps muscle. For pain relief the patients are allowed use of non-steroidal anti-inflammatory drugs (NSAIDs) and other pain-reducing products (cf. the Danish National Guidelines for knee OA [3]), as they would normally do, not needing a physician's prescription.

Outcomes

The trial is designed with four pre-determined outcome assessments; at baseline (week 0) (t_0), after 12 weeks of home-based exercise (2–8 days after the final exercise session), corresponding to the endpoint before surgery (t_1), at hospital discharge 1–8 days after surgery (t_2) (provided surgery is performed) and finally, 3 months after surgery (t_3) (Fig. 2) (provided surgery is performed). The primary endpoint is after the intervention period (t_1). Secondary endpoints of interest are just before hospital discharge 1–8 days after surgery (t_2) and 3 months after surgery (t_3).

Fig. 3 The home-based, knee-extensor strength exercise

Table 2 Exercise description

Brief name	Home-based, knee-extensor strength exercise Detailed and practical demonstration of the exercise can be accessed via this online video [30]
1. Load magnitude	Corresponding to 12 repetitions maximum (RM)
2. Number of repetitions	12
3. Number of sets	3
4. Rest between sets	Minimum 30 s, or until sufficiently recovered from previous set
5. Number of exercise interventions	Group 2 (2 sessions per week) Group 4 (4 sessions per week) Group 6 (6 sessions per week)
6. Duration of the experimental period	12 weeks
7. Fractional and temporal distribution of the contraction modes per repetition and duration (s) of 1 repetition	Concentric phase (3 s) Isometric phase (1 s) Eccentric phase (4 s) Total duration of 1 repetition (8 s)
8. Rest between repetitions	None, that is, right after finishing one repetition the next is commenced
9. Time-under-tension (TUT)	Repetition TUT (8 s) Set TUT with 12 repetitions (1 min, 36 s) Session TUT (3 sets × 12 repetitions) (4 min, 42 s)
10. Volitional muscular failure	No, but contractions should be continued until volitional muscular failure is very close. That is, until the knee-extensor muscles are maximally fatigued and the patient is not able to perform further repetitions. If volitional muscular failure occurs before the 12 RM, the resistance of the elastic band is adjusted so that the pre-determined number of repetitions can be completed
11. Range of motion	Starting position: 80–90° of knee flexion (0 = full extension) End-range of motion position: 0–10 (as close to full extension as possible)
12. Recovery time between exercise sessions	Group 2: 3 days Group 4: 1 day Group 6: 0 days
13. Anatomical definition of the exercise (exercise form)	The knee-extensor strength exercise is performed sitting in a stable chair. Sitting position in the chair is determined by the distance from the edge of the seat to the back of the knee; this distance should be 2–3 cm. If possible, the back rest can be used as well as the armrest. If the chair is without an armrest one can hold at the (side) edge of the seat. To ensure that the foot is free of the floor at 80–90° of flexion an object (e.g., a pillow) is placed under the thigh (Fig. 3). The elastic exercise band is fixated to an immoveable object (e.g., an elastic exercise band anchor behind a closed door) and wrapped around the ankle of the exercised leg (Fig. 9). Starting position: The exercise leg is relaxed with 80–90° of flexion (0 = full extension) Concentric phase: The exercise leg is extended as much as possible towards full extension using 3 s Isometric phase: The extended position is held for 1 s Eccentric phase: Slow controlled flexion of the knee joint (4 s) until the knee joint is flexed 80–90° These slow movements are chosen to ensure long time-under-tension (TUT) in the muscle

The home-based, knee-extensor strength exercise described in detail according to the mechano-biological descriptors from Toigo and Boutellier [31]

Primary outcome

Change in isometric knee-extensor strength from baseline (week 0) to after the intervention period (> 12 weeks). Knee-extensor strength is chosen as the primary outcome for the following reasons. Firstly, it is an outcome closely related to the exposure (strength training), which we consider important in a dose-response trial, because other health effects are likely mediated via increased knee-extensor strength. Secondly, knee-extensor strength is associated with the development and progression of knee OA and knee pain and function [9, 10], and as such, we also consider the outcome, a surrogate measure for the development and progression of knee OA, knee pain and function.

Secondary outcomes

Change in performance-based function (walking distance in 6 min and climbing of stairs), current knee pain and during the last week (numerical rating scale), self-reported disability (Knee Osteoarthritis Outcome Score and Oxford Knee Score) as recommended by Osteoarthritis Research Society International [33, 34], need for surgery and exercise adherence (sessions, sets, reps, TUT).

Other outcomes

Registration of adverse events (adverse event, number of adverse events in each group (surgery/no surgery).

At outcome assessment endpoint t_2 (after surgery at hospital discharge) only the outcomes *isometric knee-extensor strength, 6-Minute Walking Test (6MWT), SCT* and *current knee pain* are assessed. The *KOOS* and *OKS* questionnaires as well as *knee pain during the last week* are omitted at this endpoint as they are not validated to assess acute post-operative conditions, and use too long a recall period.

Elaborated description of outcome measures

Primary outcome

Isometric knee-extensor strength The measurement will be assessed using a computerized strength chair (Good Strength Chair, Metitur Oy, Jyvaskyla, Finland). This is a valid (0.78–0.92) and reliable (inter-trial 0.98–1.00 (standard error of measurement (SEM) < 10%), inter-evaluator 0.92–0.99 (SEM 8.34–9.92%)) knee-extensor strength measure in the TKA population [35].

Prior to outcome assessment, the patients will be informed about the procedure. The measurement consists of five maximal isometric knee-extensor contractions at 60° knee flexion separated by a 60-s pauses. The highest obtained value will be used for analysis. The patients are instructed to extend their knee as forcefully as possible with a gradual increase in force over a 5-s period. There will be strong and standardized verbal encouragement during each contraction. Knee-extensor strength will subsequently be expressed as the maximal voluntary torque per kilogram body mass (Nm/kg) using the external lever arm and body mass of each patient. Results will be presented, firstly, as absolute changes (Nm/kg) and, secondly, as relative changes (%) from baseline.

Secondary outcomes

6-Minute Walking Test for distance (6MWT) The 6MWT measures the maximal distance a patient is able to walk in 6 min between two cones placed 29 m apart from each other. The measurement has previously been found to be reliable (intraclass correlation coefficient $(ICC)_{2,1}$ 0.97, SEM 13.0 m) [36] and responsive [37] in the TKA population.

The patients are instructed to walk as long a distance as they can in six minutes. They will be encouraged to walk as fast as possible but are not allowed to jog or run. The patients are allowed to rest standing or leaning against a wall during the six minutes but the time will be running. Walking aids are allowed if needed. At each minute the patients will be informed of the time.

Stair Climb Test (SCT) The SCT measures the time (seconds) it takes to ascend and descend an 11-step flight of stairs with 16-cm step height. The stair has a handrail on both sides. The SCT has been found to be reliable in the TKA population (inter-tester $ICC_{2,1}$ 0.94–0.96, SEM 1.14 s, minimal detectable change $(MDC)_{90}$ 2.6 s) [38]. The patients are instructed to ascend and descend an 11-step flight of stairs as fast as possible, but in a safe manner. Use of hand rail and walking aid is permitted. The patients are allowed to rest during the measurement but the time keeps running.

Knee Osteoarthritis Outcome Score (KOOS) The KOOS is a 42-item questionnaire regarding knee function. The questionnaire is comprised of five subscales (symptoms (7), pain (9), function, daily living (17), function, sports and recreational activities (5) and quality of life (4). Each question has standardized answer options with five options at each question (Likert scale, 0–4). After normalization of the answers each subscale scores from 0–100 (100 indicating no symptoms). The KOOS questionnaire is found to be reliable in all subscales (pain ICC 0.8–0.97, SEM 7.2–10.2; symptoms ICC 0.74–0.94, SEM 7.2–9.0; daily living ICC 0.84–0.94, SEM 5.2–11.7; sports ICC 0.65–0.92, SEM 9–24.6; quality of life ICC 0.6–0.91, SEM 7.4–10.8) [39]. The KOOS questionnaire is also found be to reliable in the TKA population [40].

Oxford Knee Score (OKS) The OKS is a 12-item questionnaire regarding knee-related function and pain in patients with knee OA. Each question has five answer options (Likert scale, 0–4). The OKS demonstrates good test-retest reliability for both the summary scale (ICC 0.93, $MDC_{90} + 6$), pain (ICC 0.91, $MDC_{90} \pm 16$) and function (ICC 0.92, $MDC_{90} \pm 15$) component subscales [41].

Knee pain Individual knee pain is assessed with the Numeric Rating Scale (NRS). This is an 11-point subjective pain scale ranging from 0–10 (0 indicating no pain). In this trial, the patients will be asked about their knee pain related to two endpoints: (1) knee pain right now and (2) during the last week. The question is asked in the following manner "on a scale from 0 to 10 where 0 indicates no pain and 10 indicates worst imaginable pain, how much knee pain do you have (1) right now and (2) how much knee pain have you had in the last week (index knee)?" The patients are asked while seated in a chair with 70–90° of knee flexion (standardized). The NRS is found to have the strongest face validity compared to other pain measurement scales (Visual Analog Scale and Verbal Descriptor Scale) in surgical patients after surgery as well as high construct and criterion validity [42]. The NRS is also found to be reliable both before (ICC 0.82) and in the first 1–6 days following surgery (ICC 0.673–0.783) [43]. A minimal clinically important difference in pain relief post orthopedic surgery has previously been suggested to be 35% [44].

Surgical status – Need for surgery? At the second outcome assessment (after the 12-week exercise period (t_1)) the patients are asked by the outcome assessor "*based on your knee symptoms in the last week would you say that you need knee surgery?*" The outcome assessor is a physiotherapist with insight to the knee OA condition. The answer will be categorized into one of three options: (1) "*yes*" *I believe I need surgery*, (2) *I do not know* or (3) "*no*" *I do not believe I need surgery*.

Exercise adherence A large challenge regarding home-based exercise is that adherence to home-based exercise is reported to be poor [45–48], suggesting low effect of the exercise interventions. To take into account the possibility of non-adherence to the intervention (which could distort the possible conclusion that the intervention did not work), we will objectively quantify exercise adherence. Adherence to the home-based, single knee-extensor strength exercise will be assessed using a sensor (BandCizer technology) attached to the elastic exercise band used for the knee-extensor strength exercise. The sensor stores data on date, time, number of sets, repetitions, tonnage (kg × repetitions) and TUT. This elastic exercise band sensor technology has been reported to be valid [49] and reliable (ICC > 0.99) [50] for quantification of total repetition, single repetition and contraction specific TUT of an unsupervised exercise intervention.

In the present trial, patients are defined as adherent to the exercise intervention if > 75% of the prescribed exercise sessions are completed. Correspondingly, 1.5 sessions/week must be completed in group 2, three sessions/week in group 4 and 4.5 sessions/week in group 6. After the 12-week exercise period, the patients who undergo surgery are encouraged to continue exercising (same dosage) until the day of surgery. The exercise adherence during this period will also be quantified by use of the sensor. Patients deciding not to undergo surgery following the 12 weeks of exercise are encouraged to keep exercising, but exercise adherence will not be quantified. Figure 4 shows an example of objectively quantified exercise adherence via the sensor attached to the elastic exercise band. The example shows a knee-extensor strength exercise session composed of three sets with 12 repetitions in each set resulting in 36 repetitions in total for the exercise session. Number of repetitions, total TUT, mean TUT for the 36 repetition and the corresponding standard deviation can be extracted. This is also possible for single exercise sets (Fig. 5).

Adverse events All adverse events occurring while the patients are enrolled in the trial will be recorded regardless of their relation to the exercise intervention, surgery

Fig. 4 Objective quantification of exercise adherence for a full exercise session comprising three sets of 12 repetitions

Fig. 5 Objective quantification of exercise adherence for a single exercise set of 12 repetitions

or occurrence likely not related to the trial. Thus, an adverse event can both be a negative effect of the intervention, surgery or an occurrence not related to the trial, that is an untoward occurrence during the trial which may or may not causally related to the intervention or trial. Regardless of a relation to the trial, all adverse events are recorded and reported.

Finally, a qualitative study will be embedded in the trial. Semi-structured interviews will be performed with randomly selected participating patients both before and after the trial about their experienced enablers and barriers related to the knee-extensor strength exercise and adherence to the home-based intervention. The orthopedic surgeons allocated to the trial will also undergo semi-structured interviews about their experienced enablers and barriers with the non-surgical, pre-operative, home-based intervention both before and after the trial. The physiotherapists allocated to the trial will undergo focus interviews, both before the trial is commenced and once the trial is completed, to explore their experienced enablers and barriers related to administering the home-based intervention. This embedded qualitative study is undertaken to refine the home-based intervention for future trials and clinical implementation. This knowledge can then be used to design a context-specific implementation plan, given a positive trial outcome. The embedded qualitative study will be reported in a separate qualitative paper, with a clear reference to the QUADX-1 trial.

Regular auditing is planned during the trial. Regular meetings between the primary investigator, the orthopedic department, the municipalities and the research team will allow for checking of treatment notes and outcome assessment forms for fidelity to protocol which allows for addressing deviations.

Sample size

For a three-group-level One-way ANOVA of a normal mean difference with a two-sided significance level of 0.05, a common standard deviation of 0.22 Nm/kg (isometric knee-extensor strength measurement) [51], and a minimal clinically important difference of 0.15 Nm/kg (15%), a sample size of 126 (42 per group) patients is required to obtain a power of 80%. To allow for a dropout rate of 10%, we will include 140 patients in total for the intention-to-treat (ITT) analysis ($3 \times 42 + 14 = 140$).

Randomization

The patients will be randomly assigned to one of the three intervention groups (two, four or six sessions per week) by a 1:1:1 allocation ratio. The generation of the allocation sequence will be attended to by a statistician not involved in the trial in any other way. One hundred and forty opaque and sealed envelopes will be generated. After being included in the trial (signed written informed consent and completion of baseline assessment) a person independent of the trial will open one of these envelopes and inform the patient's municipality which of the three exercise groups the patient is allocated to. In this way, the allocation information is kept secret from the outcome assessor.

Blinding

The primary investigator collecting the outcomes (outcome assessor) as well as the data analysts will be blinded to allocation. At outcome assessment sessions, the outcome assessor will start by informing the patients that they are not allowed to mention what exercise dosage they have received. The data will be coded in such a way that group allocation is concealed in the dataset, thus blinding the outcome assessors and data analysts to the group allocation. The patients and the physiotherapists instructing in the intervention will not be blinded due to the nature of the intervention; however, the patients will be blinded to the exercise dosages in the other groups, which exercise dosages will be compared in the analysis and which dosage is hypothesized to have the largest effect. Unblinding will only happen in the case where the wellbeing a the patient is at risk. This will be assessed in collaboration with the patient's physician.

Data management

Data from the isometric knee-extensor strength assessment are stored on a computer dedicated to the Metitur equipment as well as being recorded in handwriting in a standardized Case Report Form. The self-reported questionnaires (KOOS and OKS) will be filled in by the patients in paper formats, as this is the way these questionnaires are designed to be filled in. All data from the functional (6MWT and SCT) and pain (NRS) assessments will be recorded on a standardized Case Report Form by the outcome assessor.

Data on exercise adherence from the sensors is saved continuously on the built-in SD card. After the intervention period, the sensors are collected and the exercise data are transferred by Bluetooth from the SD card onto a secure server. The device will not contain any personal data.

Following all outcome assessments, data will be entered into the browser-based research database Research Electronic Data Capture (RedCap 7.1.1) by trial personal using blinded double-data entry to ensure data quality. To further ensure the integrity of the data, anonymous ID numbers will be applied and data quality, data range and data values will be checked to minimize typing errors. All original written information and case report forms will be stored in a secure locker and saved for 3 after the completion of the trial at the trial location. All electronic data will be anonymous (patient IDs), coded and saved on a secure server in the Capital Region of Denmark.

Statistical analysis

Analysis outline

Three groups; group 2 = two sessions/week, group 4 = four sessions/week and group 6 = six sessions/week. There is no control group. The primary outcome is the change in isometric knee-extensor strength. Time from baseline to after 12 weeks of exercise is the primary endpoint ($\Delta_{t0\text{-}t1}$) and time from baseline to just before hospital discharge, and time from baseline to 3 months after surgery are the secondary endpoints ($\Delta_{t0\text{-}t2}$ and $\Delta_{t0\text{-}t3}$, respectively). The analysis plans for the primary and secondary analyses are outlined in Table 3.

Primary analysis

The primary analysis will be between-group contrasts for the primary outcome at the primary endpoint. Figure 6 illustrates a hypothetical presentation of changes in isometric knee-extensor strength at the primary endpoint for the three groups.

Secondary analyses

The secondary analyses will be between-group contrasts for the secondary outcomes at the primary and secondary endpoints. Figure 7 illustrates a hypothetical presentation of changes in isometric knee-extensor strength for the three groups during the whole trial period.

For all outcomes (primary and secondary), mean scores with corresponding standard deviations (SD), and between-group contrasts (change scores) with corresponding 95% confidence intervals (95% CI) and p value, will be reported at each endpoint (t_0, t_1, t_2 and t_3) for each group (groups 2, 4 and 6) (Table 4).

The patients who choose not to be operated with TKA after the exercise period will be followed with annual outcome assessments as part of a small case study.

Descriptive statistics for the trial population will be presented as in Table 5.

Supplementary analyses

The supplementary analyses will be simple regression models in which the three exercise dosage groups will be pooled, allowing us to utilize the full dataset; that is, the exercise dosage recorded by the sensors will be used in the analysis, not the prescribed exercise dosage. The dependent variables will be the change in primary and secondary outcomes from baseline to the primary endpoint and to the secondary endpoints. The independent variable will be exercise dosage, quantified in two ways: (1) as total TUT and (2) as number of completed exercise sessions for each patient (Table 6). Figure 8 illustrates a hypothetical simple regression model with the change in isometric knee-extensor strength (Nm/kg) at the primary endpoint and TUT.

Missing data

All analyses will follow the intention-to-treat (ITT) principle with a clear registration and reporting of the drop-out rate. All patients will be analyzed as randomized. To create a full analysis dataset for the intention-to-treat analyses, missing data will be imputed using multiple imputations.

Data monitoring

As the intervention(s) provided in the present trial poses little or no risk to the participating patients, no data monitoring committee will be composed. Funding sources of the current trial has no part in the design, conduction or reporting of the trial, thus there is no conflict of interests. As the intervention(s) poses little or no risk to the participating patients no interim analyses will be applied. Stopping guidelines for discontinuing and modifying the exercise has been described previously (see the "Criteria for modifying and discontinuing" section).

Table 3 Analysis outline for primary and secondary analysis

Variable/outcome	Hypothesis	Outcome measure (unit, scale)	Methods of analysis
Descriptive statistics (sample characteristics)		Age, weight, height, side of index knee (continuous and dichotomous)	Summary statistics
Primary analysis			
Primary outcome			
1. Change in *isometric knee-extensor strength* $\Delta_{t0\text{-}t1}$	Group 2 < Group 4 Group 4 ≈ Group 6	Change in Nm/kg (continuous)	Analysis of variance ANOVA[a]
Secondary analysis			
Secondary outcomes			
2. Change in *isometric knee-extensor strength* $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 ≈ Group 6	Change in Nm/kg (continuous)	ANOVA[a]
3. Change in *Knee Osteoarthritis Outcome Score* (KOOS) subscales $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in questionnaire subscales (continuous)	ANOVA[a]
4. Change in *Oxford Knee Score* (OKS) $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in questionnaire (continuous)	ANOVA[a]
5. Change in *6-Minute Walking Test for distance* (6MWT) $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in meters walked (continuous)	ANOVA[a]
6. Change in *Stair Climb Test* (SCT) $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in time used to ascend and descend stairs (continuous)	ANOVA[a]
7. Change in *current knee pain* (Numeric Rank Scale, NRS) $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in NRS 0–10 (continuous)	ANOVA[a]
8. Change in *knee pain during the last week* (Numeric Rank Scale, NRS) $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$	Group 2 < Group 4 Group 4 > Group 6	Change in NRS 0–10 (continuous)	ANOVA[a]
9 Distribution in *need for surgery*	Group 2 < Group 4 Group 4 > Group 6	Yes, don't know, no	Summary statistics
Other outcomes			
10. Difference in *adherence to intervention* between groups	Group 2 > Group 4 Group 4 > Group 6 Group 2 > Group 6 We hypothesize differences between groups in adherence (%) to the training intervention (i.e., higher number of sessions per week, the lower adherence (%))	Number of sessions, sets, repetitions and time-under-tension	ANOVA[a]

[a]If data are not normally distributed the non-parametric Kruskal-Wallis test will be used
Analysis of variance: (ANOVA)

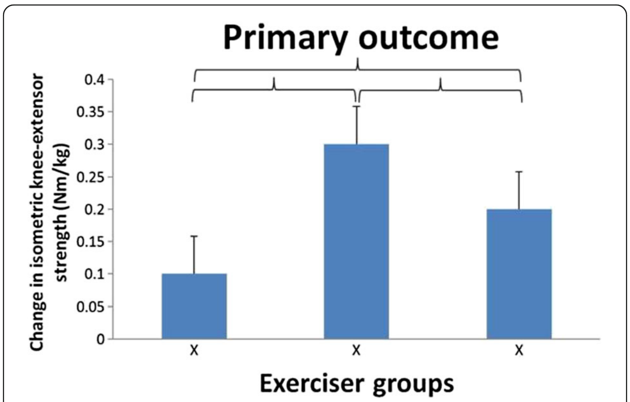

Fig. 6 A hypothetical presentation of group changes from baseline to the primary endpoint (after 12 weeks of exercise) for the primary outcome, knee-extensor strength

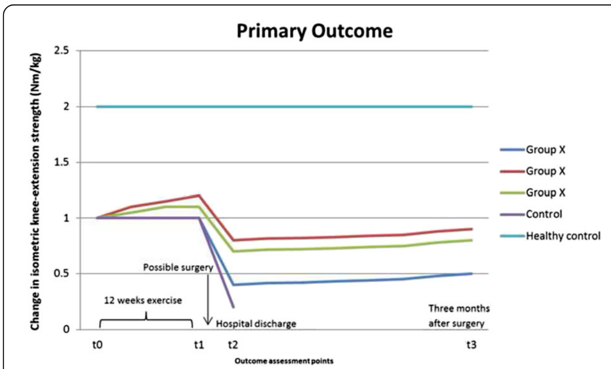

Fig. 7 A hypothetical presentation of group changes in knee-extensor strength over the whole trial period. NB, control data are from the academic literature [11] and so are the healthy, age-matched, control data (age 66.8 years (6.5 SD)) [7]

Table 4 Outcomes for primary and secondary analyses

	t_0 Baseline			t_1 After 12-week exercise			t_2 After surgery at hospital discharge			t_3 3 months after surgery			Between-group contrasts (change scores) 95% CI (*p*)
Mean, SD	Gp. 2	Gp. 4	Gp. 6	Gp. 2	Gp. 4	Gp. 6	Gp. 2	Gp. 4	Gp. 6	Gp. 2	Gp. 4	Gp. 6	
Isometric knee-extensor strength (Nm/kg)													Primary analysis $\Delta_{t0\text{-}t1}$ Secondary analysis $\Delta_{t0\text{-}t2,\ t0\text{-}t3}$
6-Minute Walking Test for distance (6MWT)													Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$
Stair Climb Test (SCT)													Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$
Knee Osteoarthritis Outcome Score (KOOS)							Na	Na	Na				Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$
Oxford Knee Score (OKS)							Na	Na	Na				Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$
Current knee pain (Numeric Rating Scale (NRS) 0–10)													Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$
Knee pain during the last week (NRS 0–10)							Na	Na	Na				Secondary analysis $\Delta_{t0\text{-}t1}$, $\Delta_{t0\text{-}t3}$
Need for surgery now (yes/don't know/no)	Na	Na	Na				Na	Na	Na	Na	Na	Na	Secondary analysis
Exercise adherence													
• No. sessions (prescribed, completed, % completed)	Na	Na	Na							Na	Na	Na	Secondary analysis
• Seconds of total time-under-tension (TUT) (prescribed, completed, % completed)	Na	Na	Na							Na	Na	Na	Secondary analysis
Adverse events													Secondary analysis

Access to the final trial dataset

The principal investigator and principal supervisor will have full access to the dataset as well as all co-authors. A fully patient-anonymized dataset and corresponding statistical analysis code will be made available for the scientific journal reviewing the manuscript and its results within 6 months in line with the recent proposal from the International Committee of Medical Journal Editors (ICMJE) [52].

Ancillary and post-trial care

The current trial is not planned to include patient ancillary care or post-trial care. On completion of the trial, if participants want to continue with the exercises independently they can do so. However, this will not be a part of the trial and will be on the patient's own initiative.

Table 5 Descriptive statistics

	Gp. 2	Gp. 4	Gp. 6	All patients
Age (years)				
Height (cm)				
Weight (kg)				
Gender (m/f)				
Index knee (r/l)				
Kellgren-Lawrence classification (I–IV)				

Dissemination policy

The QUADX-1 trial is planned to be reported in three manuscripts, which will be published in scientific peer-reviewed journals. All manuscripts will refer to the QUADX-1 trial's Clinical.Trials.gov identifier. The first manuscript will be the trial protocol, the second manuscript will be the primary trial report of the investigated dose-response relationship, and the third manuscript will be a qualitative study investigating enablers and barriers for patient adherence to home-based exercise and physiotherapists' experience in administering home-based exercise before TKA. The results will also be presented at relevant scientific conferences and symposiums. Trial participants will be informed of the trial via a letter explaining the results in layman's terms. On request, the data underlying the results presented in the manuscript will be available to reproduce the findings. We intend to make the dataset – containing de-identified individual patient data – publicly available no later than 6 months after publication, consistent with the recent proposal from the International Committee of Medical Journal Editors (ICMJE) [52], if it complies with national

Table 6 Regression models for supplementary analysis

Supplementary analyses (primary outcome at primary endpoint)		
	Dependent variable (y)	Independent variable (x)
Linear regression model	Change in *isometric knee-extensor strength* $\Delta_{t0\text{-}t1}$	Exercise adherence Seconds of total time-under-tension (TUT) Number of completed exercise sessions
Supplementary analyses (secondary outcomes at primary and secondary endpoints)		
Linear regression models	Change in *isometric knee-extensor strength* $\Delta_{t0\text{-}t2}$, $\Delta_{t0\text{-}t3}$	Exercise adherence Seconds of total time-under-tension (TUT) Number of completed exercise sessions
	Change in *6-minute walk test for distance* (6MWT) $\Delta_{t0\text{-}t1,\ t0\text{-}t2,\ t0\text{-}t3}$	
	Change in *stair climb test* (SCT) $\Delta_{t0\text{-}t1,\ t0\text{-}t2,\ t0\text{-}t3}$	
	Change in *Knee Osteoarthritis Outcome Score* (KOOS) subscales $\Delta_{t0\text{-}t1,\ t0\text{-}t3}$	
	Change in *Oxford Knee Score* (OKS) $\Delta_{t0\text{-}t1,\ t0\text{-}t3}$	
	Change in *current knee pain* (Numeric Rating Scale, NRS) $\Delta_{t0\text{-}t1,\ t0\text{-}t2,\ t0\text{-}t3}$	
	Change in *knee pain during the last week* (Numeric Rating Scale, NRS) $\Delta_{t0\text{-}t1,\ t0\text{-}t3}$	
	Need for surgery (yes/don't know/no)	
	Averse events	

regulations, e.g., the Danish Data Protection Agency. Trial data can be requested by contacting the main investigator (RSH) or trial director (TB). Positive as well as negative and inconclusive results will be published.

All contributors to the study will be offered to co-author the three above manuscripts if they fulfill the International Committee of Medical Journal Editors (ICMJE) recommendations for authorship [52]. No professional writers will be used.

Discussion

In 2011, approximately 60,000 patients were registered in the Danish health care system with symptoms of knee OA and the annual incidence of knee OA has increased from 35.8 in 1997 to 155.2 in 2010 per 100,000 inhabitants [3]. Consequently, this population is very large and growing, which stresses the importance of optimizing the treatment offered to these patients. The *QUADX-1 trial* will add knowledge relating to which knee-extensor strength exercise dosage is most effective in increasing knee-extensor strength and whether a single, home-based (unsupervised) knee-extensor strength exercise is feasible in patients with end-stage knee OA.

The minimal treatment approach (single exercise) has been chosen as it is a pragmatic and time-saving solution [46]. Further, the rationale for investigating a home-based, single knee-extensor strength exercise is that it could improve exercise adherence as it is simple (minimal intellectual effort), does not take a long time (requires less surplus energy) and is likely to inflict less pain (less stress imposed on the knee joint). An exercise targeting the knee-extensor muscle is chosen as it is the single most important muscle for function in the knee OA population [9, 10, 13, 14].

In summary, the objective of the *QUADX-1 trial* is to investigate the efficacy of three different exercise dosages of pre-operative, home-based, knee-extensor strength exercise before and shortly after surgery in patients eligible for total knee replacement. The results will indicate which knee-extensor strength exercise dosage is most effective for increasing knee-extensor strength in the end-stage knee OA population. Furthermore, the results will indicate whether pre-operative knee-extensor strength exercise improves knee-extensor strength and function prior to surgery and whether this effect (if any) is sustained following surgery.

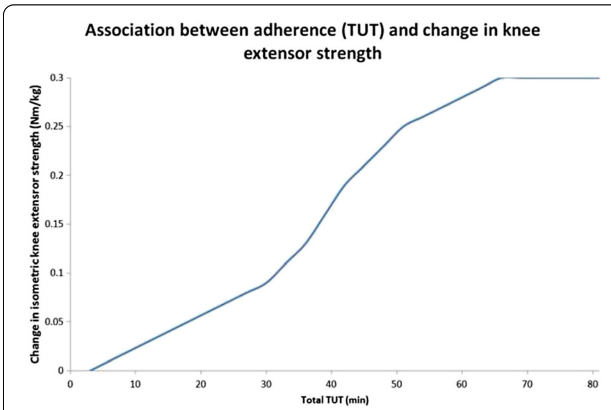

Fig. 8 A hypothetical simple regression model with the change in isometric knee-extensor strength (Nm/kg) at the primary endpoint and time-under-tension (TUT)

Fig. 9 Elastic exercise band fixation to an immoveable object (e.g., an elastic exercise band anchor behind a closed door) and placement around the ankle of the exercise leg

Strengths

The trial design has several strengths as it addresses numerous gaps in the academic literature. Trials investigating the dose-response relationship of strength exercise in patients with end-stage knee OA are rare. Accordingly, there is a need for investigating the most effective exercise dose in this patient population, as highlighted in two recent systematic reviews using meta-analysis [21, 22]. Peer et al. highlight the scarcity of evidence related to exercise dose-response in patients with knee OA needed to guide pre-habilitation in clinical practice [22]. Further, Bartholdy et al. suggest that a 30–40% gain in knee-extensor strength is needed to positively affect pain and disability in patients with knee OA [21], highlighting the need for evidence to suggest the exercise dosage required to obtain adequate improvement in knee-extensor strength.

Adherence to home-based exercise is reported to be low with a high risk of over-reporting [45–48]. The use of sensors attached to the elastic exercise band will address this in an objective manner. Further, in a recent systematic review on adherence with physiotherapy exercises it was requested that the relationship between adherence and treatment outcome was investigated [46].

The exercise regimes currently offered to patients with knee OA are mostly supervised exercise sessions at outpatient clinics and comprise several exercises resulting in accumulated time spent and cost. In this trial, a single, simple, home-based exercise is applied, thus, investigating whether an alternative exercise treatment, which is simplified and maintained unsupervised at home, might be offered to these patients.

This trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist (Fig. 2, Additional file 1) [24] and the exercise intervention is reported according to the TIDieR Checklist (Additional file 2) [26] allowing for replication and direct clinical use, which has been requested in a recent review [53]. The cross-sectional design mimics everyday practice of cross-sector boarder communication increasing the external validity for future clinical implementation.

Limitations

The trial has some limitations which must be taken into consideration. There is no control group limiting the inferences that can be made on the effect of the knee-extensor strength exercise.

Due to the nature of the intervention (exercise) there is a risk of selection bias, e.g., patients motivated for exercise are more likely to participate in the trial. This also limits the external validity with respect the whole knee OA population.

In the present trial design, the patients are asked about their *need for surgery* after the 12-week exercise period. In line with the above limitation, the answer to this question could be biased as patients motivated for exercise might be less motivated towards surgery affecting their answer to *need for surgery* towards.

Though the sensor objectively measures activity with the elastic exercise band, the sensor cannot measure who is exercising, which muscle is exercised or what movement is performed.

Finally, no recording or monitoring of the use of knee-related pain medication during the trial is planned for.

Trial status

Protocol version no. 4.1 (21 November 2017). Inclusion began 1 November 2016. Approximate date for inclusion completion is 31 December 2019.

Additional files

Additional file 1: SPIRIT Checklist. (DOC 122 kb)

Additional file 2: TIDieR Checklist. (DOCX 31 kb)

Additional file 3: Patient brochure (English). (PDF 825 kb)

Additional file 4: Administrative information. (DOCX 38 kb)

Abbreviations

6MWT: 6-Minute Walking Test; ASA: American Society of Anesthesiologists' physical status classification; ICC: Intraclass correlation coefficient; ITT: Intention-to-treat; KOOS: Knee Osteoarthritis Outcome Score; MDC: Minimal detectable change; Nm/kg: Newton-meter (torque) per kilogram body mass; NRS: Numeric Rating Scale; OA: Osteoarthritis; OKS: Oxford Knee Score; RM: Repetitions-maximum; SCT: Stair Climb Test;

SEM: Standard error of measurement; TKA: Total knee arthroplasty; TUT: Time-under-tension

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Funding
The Capital Region's strategic funds (1,500,000 dkkr (financial)) and the Capital Region's fund for cross-continuum research (500,000 dkkr (financial)). Funding sources of the current trial have had no part in the design, conduction or reporting of the trial, thus there is no conflict of interests.

Availability of data and materials
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. A fully patient-anonymized dataset and corresponding statistical analysis code will be made available for the scientific journal reviewing the manuscript and its results within 6 months. Contact: Rasmus Skov Husted (rasmus.skov.husted@regionh.dk) and Thomas Bandholm (thomas.quaade.bandholm@regionh.dk) (Additional file 4).

Authors' contributions
TB drafted the original idea for the trial and initiated the trial design. AT, KT, MSR, HH and RSH later contributed to the trial design process. TB and RSH drafted the trial protocol and all other authors contributed and approved the final version of the protocol. TB is the main grant holder and responsible for the completion of the trial. RSH is the trial manager and principal investigator responsible for daily operation, coordination between trial collaborators, outcome assessment of patients, collection and structuring of data, ensuring compliance with milestones and completion of the trial. RSH will draft the manuscripts for publication with contribution and approval of the final version from all co-authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethical approval has been granted by the Ethical Committee of the Capital Region Denmark. ID: H-16025136. Confirmation received 13 September 2016. Informed consent will be obtained from all participants of the trial.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Physical Medicine and Rehabilitation Research - Copenhagen (PMR-C), Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [2]Department of Physical and Occupational Therapy, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [3]Optimed, Clinical Research Centre, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [4]Clinical Orthopedic Research Hvidovre (CORH), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [5]Sports Orthopaedic Research Center – Copenhagen (SORC-C), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [6]Research Unit for General Practice in Aalborg, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark. [7]Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark.

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Manuscript IV

Perceived facilitators and barriers among physical therapists and orthopedic surgeons to pre-operative home-based exercise therapy with *one* exercise-only in patients with severe knee osteoarthritis: A qualitative interview study nested in the QUADX-1 trial

Rasmus Skov Husted, Thomas Bandholm, Michael Skovdal Rathleff, Anders Troelsen and Jeanette Kirk

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Title

Perceived facilitators and barriers among physical therapists and orthopedic surgeons to pre-operative home-based exercise with *one* exercise-only in patients with severe knee osteoarthritis: A qualitative interview study nested in the QUADX-1 trial

Rasmus Skov Husted[1,2]*, Thomas Bandholm[1,2], Michael Skovdal Rathleff[3,4], Anders Troelsen[5] and Jeanette Kirk[1,2]

[1]Clinical Research Centre, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[2]Physical Medicine & Rehabilitation Research-Copenhagen (PMR-C), Department of Physical and Occupational Therapy, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[3]Research Unit for General Practice in Aalborg, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[4]Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark
[5]Clinical Orthopedic Research Hvidovre (CORH), Department of Orthopedic Surgery, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
*Corresponding author: rasmus.skov.husted@regionh.dk

Abstract

Aim

Clinical guidelines recommend non-surgical treatment before surgery is considered in patients eligible for knee replacement (KR). Surgical treatment is provided by orthopedic surgeons and exercise therapy is provided by physical therapists. This study aimed to investigate key stakeholder perspectives on pre-operative, home-based exercise therapy with *one* exercise-only in patients eligible for KR.

Methods

This qualitative study is embedded within the QUADX-1 randomized trial that investigates a model of coordinated non-surgical and surgical treatment for patients eligible for KR. Physical therapists and orthopedic surgeons working with patients with knee osteoarthritis in their daily clinical work were interviewed (one focus group and four single interviews) to explore their perceived facilitators and barriers related to pre-operative home-based exercise therapy with *one* exercise-only in patients eligible for KR. Interviews were analyzed using content analysis.

Results

From the content analysis three main themes emerged: 1) *Physical therapists' and orthopedic surgeons' ambivalence in their professional roles,* 2) *Orthopedic surgeons view on exercise,* and 3) *Coordinated non-surgical and surgical care.*

Conclusion

We found that the pre-operative exercise intervention created ambivalence in the professional role of both the physical therapists and orthopedic surgeons. The physical therapists were skeptical towards over-simplified exercise therapy. The orthopedic surgeons were skeptical towards the potential lack of (long-term) effect of exercise therapy in patients eligible for KR. The consequence of these barriers and ambivalence in the professional role is important to consider when planning implementation of the model of coordinated non-surgical and surgical treatment.

Trial registration: ClinicalTrials.gov, ID: NCT02931058.

Introduction

Knee osteoarthritis (OA) is a growing challenge for the health care system and more knee replacements (KR) are performed each year to treat the condition with an estimated increase of 69% from 2012 to 2050 in the United States (1,2). A key feature of knee OA is knee pain which is often associated with decreased quality of life, physical activity and muscle strength. Due to pain and physical impairments it may increase the risk of sick leave and early retirement (3,4). Traditionally, patients eligible for KR are provided highly specialized surgical treatment to help overcome their knee OA-related pain and concomitant symptoms (5,6). Patients, not eligible for KR, can be referred to non-surgical treatments such as exercise therapy and weight loss (7). Both international and national guidelines recommend non-surgical treatment (i.e. exercise therapy and weight loss) before surgery is considered (7,8). Despite this, it is estimated that up to 25% of patients could be inappropriately receiving KR prior to the recommended non-surgical treatment (9).

Exercise therapy is generally provided by physical therapists and most often consists of different exercises (an exercise program) which can be supplemented with other treatment modalities, such as e.g. manual therapy (10–12). This supervised and group-based organization of treatment enables physical therapists to interact and to engage themselves to a great extent in the treatment of their patients, creating a strong physical therapist-patient relationship (13). This high level of engagement is possible because physical therapists spend a relatively long time with the patients during an exercise session (13). This is in contrast to orthopedic surgeons who only have limited time with patients in their out-patient clinic to assess the need for surgical treatment (13,14).

Improving the coordination of treatment across health care sectors is vital in order to improve outcomes for patients with knee OA (15) – and it can be achieved. For example, rehabilitation exercise therapy after KR is coordinated across health care sectors in current clinical practice. This is not the case for the treatment of patients with knee OA who are potential candidates for KR. Optimally, orthopedic surgeons should refer patients potentially eligible for KR to initial non-surgical treatment (e.g. exercise therapy) in their municipality - according to guideline recommendations (7,8) and then re-evaluate the need for surgical treatment by shared decision making, based on changes in symptoms (16). In order to organize a coordinated care pathway like this, stakeholder involvement is fundamental (17).

Involving stakeholders will help identify and manage facilitators and barriers related to the coordinated care pathway under study (18). In the care of patients with knee OA, the stakeholders in daily clinical work are the orthopedic surgeons and physical therapists. Thus, their views and thoughts on a new care initiative are highly important if this one initiative is to be effectively implemented and adopted in clinical practice (19).

Previous reports investigating facilitators and barriers among orthopedic surgeons suggest a number of challenges in the use of non-surgical treatment in patients with knee OA (15,20). For example, “No effect of physical therapy when there is an obvious loss of cartilage” and “Lack of visibility into physical therapies” were associated with decline in referrals to physical therapy and reported as a barriers (15). In the way that surgery is considered important for the profession of orthopedic surgery (5), exercise therapy is considered important for the profession of physical therapy (13,21). However, a study in patients with shoulder pain, suggests that physical therapists have barriers concerning simplified exercise interventions (21), that is, interventions with a minimal number of exercises and limited consultation time between the physical therapist and patient. The above implies that orthopedic surgeons and physical therapists may have barriers concerning coordinated non-surgical care in the form of simplified pre-operative exercise therapy in patients eligible for KR. Context-specific screening for facilitators and barriers is important to help facilitate implementation in clinical practice and optimize coordination of treatment (22,23).

Aim

The aim of this study was to identify perceived facilitators and barriers – among orthopedic surgeons and physical therapists – towards coordinated non-surgical and surgical treatment of patients with severe knee osteoarthritis using pre-operative home-based exercise therapy with *one* exercise.

Methods

Context: The QUADX-1 trial

This qualitative study is an embedded part of a "parent" randomized trial (the QUADX-1 trial) investigating the dose-response relationship of pre-operative exercise therapy prior to potential KR in patients with severe knee OA (24). The trial employs a model of coordinated non-surgical and surgical treatment where orthopedic surgeons re-evaluate patients' need for surgery following exercise in the municipality. In the Danish health care system, non-surgical treatment is performed in the municipalities and surgical treatment is performed at the hospitals. To ensure coherent care pathways with high quality for patients, cross-sector coordination of treatment is essential. In the QUADX-1 trial, the patients exercise unsupervised at home for twelve weeks after an initial exercise instruction by a physical therapist. At four and eight weeks, the patients have follow-up consultations with the physical therapist. The project is designed as an intervention trial with concurrent gathering of information for clinical applicability and implementation (the present qualitative study), also referred to as a hybrid design I (25). The exercise intervention consists of *one* muscle strengthening exercise – seated knee-extensions using an elastic exercise band as resistance. This *one* specific exercise was chosen based on the concept of "less is more", as it was considered pragmatic and simple. That is, it is easy to set up at home, easy to remember how to perform, requires little intellectual effort and is easy to master. Further, an exercise intervention comprising *one* exercise was chosen as compliance to home-based exercise is reported to be poor (26–29) and an intervention of one exercise could increase adherence. Additional details on the QUADX-1 trial and the *one* knee-extension exercise is available in the published open access trial protocol (24).

Design

This qualitative study involves the analysis of data collected during interviews with the two main stakeholders: orthopedic surgeons and physical therapists. Interview is a recognized qualitative method for obtaining in-depth knowledge about stakeholder's feelings, experiences and attitudes (30,31). We performed interviews to understand the perceived barriers and facilitators among the orthopedic surgeons and physical therapists regarding this novel coordination of surgical and non-surgical treatment prior to the beginning of the parent trial. The qualitative study is reported according to the Standards for Reporting Qualitative Research: A Synthesis of Recommendations (SRQR) checklist (32) (Appendix 1).

Study setting

The study was carried out in Denmark, where the health care system is publicly funded from taxes, enabling the Danish welfare state to provide free treatment for all citizens. The orthopedic department where this study was performed is an integrated part of the hospital and has more than 45,000 ambulatory visits and around 7,000 operations are performed every year. All municipalities have rehabilitation centers where patients are referred to outpatient rehabilitation subsequent to treatment at the hospital, for example KR.

Recruitment and study participants

We recruited six physical therapists from three municipalities and four orthopedic surgeons from one hospital involved in the QUADX-1 trial (24). All participants had to be involved in the QUADX-1 trial, as the intervention under study was not implemented in routine clinical practice. Thus, the six physical therapists and four orthopedic surgeons represents all possible participants. Participants were contacted by the primary investigator and interview moderator (RSH) by e-mail with an invitation to participate in the interviews. RSH sent the invitations because he would be conducting the interviews. All invited participants accepted. All eligible physical therapists had daily clinical work with patients diagnosed with knee OA and rehabilitation following KR. All eligible orthopedic surgeons had daily clinical work with patients potentially eligible for KR due to knee OA symptoms. A random sample of patients participating in the QUADX-1 trial were also interviewed about their perceptions of facilitators and barriers towards coordinated non-surgical and surgical treatment using pre-operative home-based exercise therapy with *one* exercise. This work is as yet unpublished.

Interviews: Focus group and single interviews

We aimed to use focus group interviews for all participants as the purpose of the interviews was to explore the perceived facilitators and barriers and associated feelings, experiences and attitudes of the health care professionals on the coordinated non-surgical and surgical treatment investigated in the QUADX-1 trial. Focus group methodology is considered an appropriate method for this purpose because participants can freely express and discuss their experiences as well as listen to the experiences of the other participants. It is therefore particularly suitable to collect data on social groups, interactions, interpretations and norms (30,31,33). We completed the focus group interview with the physical therapists as planned, but it proved practically impossible with the orthopedic surgeons due to very tight work schedules. As a compromise, we conducted single interviews instead because this method is suitable for producing in-depth data on a particular phenomenon or topic (34). Both the focus group interview and the single interviews were guided by semi-structured interview guides with open-ended questions (Appendix 2 and 3). A "funnel approach" was used at all interviews starting with broad open-ended questions followed by probing and sensitizing questions aiming to elicit deeper and more detailed information (30).

Procedures

The interviews took place before the first patient was enrolled in the QUADX-1 trial to ensure no experience with the trial among the participants. Thus, the interviews only relate to their preconceptions and not later experiences during the trial. The interviews took place in meeting rooms at a hospital in the Greater Copenhagen area, Denmark. The two interview guides were developed in an iterative process by RSH, TB and JK informed by literature and clinical experience to steer the interviews towards the phenomena of interest. Before the interviews, the two interview guides were piloted by RSH and JK in two single interviews with health care professionals to revise poorly formulated questions after which they were re-piloted. The focus group interview lasted two hours (including two breaks) and the single interviews lasted between 30 and 40 minutes. At the focus group interview, the moderator (RSH) facilitated the dialogue while JK observed the interview and took notes of topics important to pursue. RSH and JK went through these notes in the two breaks in the focus group interview and adjusted the interview to ensure that these topics were included (e.g. topics not pursued by RSH due to preconception as a physical therapist). The single interviews were conducted by RSH and at the first single interview, JK observed and took notes of important topics, which were used to qualify the following interviews. Following every interview, RSH and JK listened to the audio file and adjusted the interview guide based on new important topics. The interviews were recorded with a digital voice-recorder (Philips Voice Tracer LFH0882) and afterwards transcribed verbatim by RSH.

Data analysis

Fully transcribed interviews were brought together into one text constituting the unit of analysis. Before analyzing the interviews, RSH read the data material through several times to obtain a sense of the whole. The transcribed interviews were analyzed by RSH and JK using inductive thematic analysis to group the data into sub-themes and themes (35). The analytical process involved 1) dividing the text into meaning units, 2) condensing meaning units, 3) abstracting and coding the condensed meaning units, 4) sorting codes based on similarities and differences, 5) sorting codes into sub-themes and themes. Tentative sub-themes/themes were discussed by RSH, TB and JK through a process of reflection and discussion. These discussions facilitated an iterative process in which RSH and JK re-analyzed meaning units and codes and re-coded the data based inputs from the discussions (36). Themes were then revised and agreed on to strengthen the validity of the results. 6) Finally, the latent content (underlying meaning) of the sub-themes was formulated into themes (35). The final themes were discussed and agreed upon by all members of the research team (Table 1). Through this process, it was possible for RSH to put his preconception in dialogue with the text (fusion of horizons). Thus, the understanding of physical therapists and orthopedic surgeons perceived facilitators and barriers towards coordination of surgical and non-surgical treatment gradually changed (37).

Meaning unit	**Condensed meaning unit: description close to the text**	**Condensed meaning unit: interpretation of the underlying meaning**	**Sub-theme**	**Theme**
Physical therapist 2, focus group interview: "*Well, I have been thinking. They (the patients) come for instruction in only one exercise and we are not supposed to consider all the other things. Eh, all the questions they might have regarding other painful areas of their body, whatever the reason. I have certainly been thinking that I wanted to examine them more closely in general and in relation to their knee OA. Yes, now it's only this one exercise they get.*"	The physical therapists are only supposed to give instructions in one exercise. Not consider other questions or disorders the patients might have.	The physical therapists want to examine the patients for other disorders and not only provide instruction for one exercise.	Professional role as a physical therapist is simplified.	Physical therapists' ambivalence in their professional role.

Table 1: Example of inductive thematic analysis to group data into sub-themes and themes as described by Graneheim and Lundman (35).

Ethics

The study was performed according to the Helsinki Declaration (38). Participants were informed that participation in the interviews was voluntary and that they could withdraw consent at any time during the interview. All invited participants were allowed a minimum of 24 hours to consider participation. All participants were informed about anonymity and confidentiality and gave oral consent to participate prior to the interviews. All participants are pseudo-anonymized and reported data are de-identified (no mentioning of names, age or gender). Data were stored on a file drive secured by log-in. The study has been approved by The National Committee on Health Research Ethics (Protocol no.: H-16025136).

Results

The thematic analysis showed three main themes: 1) *Physical therapists' and orthopedic surgeons' ambivalence in their professional roles,* 2) *Orthopedic surgeons view on exercise,* and 3) *Coordinated non-surgical and surgical care.* These themes emerged from the thematic analysis and contain nine sub-themes. These sub-themes were; 1) *Supporting patient self-management is a physical therapy core skill*, 2) *Professional role as a physical therapist is simplified*, 3) *Skepticism towards one home-based exercise, 4) Must believe in exercise as treatment for patients with severe knee OA*, 5) *Patient preferences*, 6) *Skepticism towards (long-term) effect of exercise*, 7) *Different purposes of referring a patient to exercise*, 8) *Orthopedic surgeons' skepticism to the content of the exercise treatment they refer to* and 9) *Responsibilities in coordinated care and engagement in the care pathway*. The themes and sub-themes represent different facilitators and barriers among orthopedic surgeons and physical therapists towards home-based pre-operative exercise in patients eligible for KR.

No.	**Themes**	**Sub-themes**
1	Physical therapists' and orthopedic surgeons' ambivalence in their professional roles	Supporting patient self-management is a physical therapy core skill
		Professional role as a physical therapist is simplified
		Skepticism towards one home-based exercise
		Must believe in exercise as treatment for patients with severe knee OA
		Patient preferences
2	Orthopedic surgeons view on exercise	Skepticism towards (long-term) effect of exercise
		Different purposes of referring a patient to exercise
3	Coordinated non-surgical and surgical care	Orthopedic surgeons' skepticism to the content of the exercise treatment they refer to
		Responsibilities in coordinated care and engagement in the care pathway

Table 2: Themes and associated sub-themes from the inductive thematic analysis.

Theme 1 – Physical therapists' and orthopedic surgeons' ambivalence in their professional roles

Among the physical therapists' and orthopedic surgeons' different sub-themes relate to how coordinated non-surgical and surgical care with home-based exercise therapy with *one* exercise creates ambivalence in their professional roles. Ambivalence is defined as a condition that occurs when you have two conflicting feelings or attitudes at the same time. With ambivalence you will have difficulty making decisions, as all solutions seem equally good or equally bad (39).

Physical therapists

Exercise therapy is a central treatment modality in the physical therapy profession, not least in the treatment of patients with knee OA. Most exercise therapy is organized in group sessions where physical therapists monitor and adjust treatment closely, allowing a high degree of engagement in the treatment. However, in the interviews it turned out that the physical therapists recognize the importance of supporting patient self-management to complement supervised exercise therapy.

Sub-theme 1: Supporting patient self-management is a physical therapy core skill

One sub-theme that emerged from the focus group interview was that the physical therapists are conscious about the importance of educating and providing patients with tools to self-manage their condition. In patients with chronic conditions (e.g. knee OA) self-management is especially important if the effect of treatment is to be sustained following supervised exercise. Exercise is likely a life-long treatment in patients with knee OA making provision of supervised exercise unrealistic, again underlining the importance of patient self-management. The following excerpt illustrates the physical therapists' attitude towards this:

"*We are focused on this (self-management) right from the beginning. At the same time, we tell them (the patients) that rehabilitation is not finished after an interim exercise program in the municipality and that it is necessary to continue exercising to get the* *full benefit.*" (Physical therapist 2, focus group interview).

The physical therapists mention the importance of ensuring patient adherence to exercise and teaching patients how to adjust their treatment (exercise) properly in line with their symptoms. Different pedagogic approaches were discussed between the physical therapists to achieve this. Typically, this is a process going from a lot of supervision and guidance towards less and less as the patients become independent. One physical therapist expresses:

"*I think that one of my greatest tasks, together with the patient, is to make the patient independent so that they are able to manage without me when they have finished supervised treatment… I think this one of the most important tasks. It is something we focus on right from the moment they come through the door.*" (Physical therapist 1, focus group interview).

As the physical therapists are aware of this, they embrace this skill and express that it is important to give patients a sense of responsibility for their own treatment and to teach them principles of self-management of their condition. In this way, even though they distance themselves from the patients, they keep some control over the patient's treatment.

Sub-theme 2: Professional role as a physical therapist is simplified

In the present trial, the diagnosis and treatment are already defined, meaning that the physical therapists do not need to clinically examine the patients. They can go right ahead and instruct the patients on how to do the *one* exercise at home. The role of the physical therapist becomes (somewhat) predefined and pedagogical compared to more traditional clinical practice with frequent adjustments to treatment. This was mentioned as unusual practice by the physical therapists:

"Well, this limitation I have been given and the desire to carry out an examination, and other things which you now have to avoid, is an unusual role that you have to get used to." (Physical therapist 3, focus group interview).

The limited face-to-face contact between patient and physical therapist where they only see each other three times over the course of three months, gives rise to several concerns among the physical therapists. They express concern about the quality (and thus effectiveness) of the exercise (treatment) when it is primarily home-based as they are not there to ensure high quality in the exercises and provide timely adjustments. Related to this is a concern about the limited number of predefined consultations with the possibility of supervising and adjusting the exercise. A physical therapist explained:

"Well, I have been thinking. They (the patients) come for instruction in only one exercise and we are not supposed to consider all the other things. All the questions they might have regarding other painful areas of their body, whatever the reason. I have certainly been thinking that I wanted to examine them more closely in general and in relation to their knee OA. Yes, now it's only this one exercise they get." (Physical therapist 2, focus group interview).

The predefined and advisory role with a limited number of consultations challenges and simplifies their professional role and, thus, becomes a potential barrier.

Despite the above-mentioned barriers regarding simplified home-based exercise, there was broad consensus among the physical therapists that it is good to have two treatment options (supervised and home-based). A physical therapist said:

"*Yes, and it is not as if you can say it is good for everyone. It is good for some yes. And it is good for those who don't want to be absent from work or who would like to stay in their holiday house, and therefore cannot come to the gym. And where we can also see that the exercise is done satisfactorily. But it is definitely not for everyone"*. (Physical therapist 1, focus group interview).

This discussion substantiates that not all patients are candidates for home-based exercise according to the physical therapists, which also supports the option of a stratified treatment approach (two treatment options). The possibility of two treatment options and thus a better chance of providing treatment suiting individual patient preferences becomes a potential facilitator.

Sub-theme 3: Skepticism towards one home-based exercise

The physical therapists express concern regarding exercise treatment with *one* exercise as they think it is a rigid treatment limiting usage of their professional skills. One physical therapist expressed:

"Well, everything depends on <u>this one exercise</u> *you know."* (Physical therapist 6, focus group interview).

The physical therapists discussed the possibility of changing the exercise (e.g. if performed with low quality) or add more exercises based on the patient's symptom response and preferences. The physical therapists explained that this is how "normal" clinical practice is carried out and an integrated part of the physical therapists' professional work. This was shown in statements such as this:

"*Well, often something (an exercise) is effective, but if you find out that it is not, then you know that you have other exercises which would be effective, and you might well add these to the exercise program.*" (Physical therapist 6, focus group interview).

A home-based single exercise intervention without the option of exercise adjustment or the addition of other exercises becomes a barrier to physical therapists because of their professional self-image.

However, they also discuss two facilitators related to the *one* home-based exercise approach. Providing patients with *one* exercise keeps the intellectual effort required to a minimum while also taking less time to complete. The physical therapists describe the exercise as tangible, which could increase patient ownership of the exercise, potentially leading to improved exercise adherence and thereby, treatment effect. One physical therapist stated:

"*I think it is a very tangible exercise they (the patients) have to go home and do, and it is also easy. And I think this must be good for the patient…. That there are not so many questions when they get home. How was I was supposed to do the exercise?... I think this* *actually is a strength with the exercise.*" (Physical therapist 1, focus group interview).

In continuation of this, the physical therapists also mention that the *one* exercise could be very important:

"We only give them one exercise, they don't have anything else. I think this is the reason they get it done… Also, the fact that they have one exercise. This makes it very important." (Physical therapist 3, focus group interview).

In summary, a single exercise home-based intervention creates a dilemma among the physical therapists. On the one hand the physical therapists perceive *the importance of providing patients with tools for self-management, the advantage of having two treatment options to meet patient preferences* and *the potential advantages of providing patients with only one exercise* as facilitators for implementing the one exercise. These factors support the simplified treatment approach among the physical therapists and their view on their professional role. On the other hand, the physical therapists believe that the simplified treatment approach *simplifies their professional role*, *limits contact time with patients* and *providing only one exercise limits use of professional skills.* This challenge the physical therapists creating ambivalence in their professional role.

Orthopedic surgeons

All the orthopedic surgeons are aware that clinical guidelines recommend non-surgical treatment (e.g. exercise therapy and weight loss) in all patients before surgical treatment is considered. An orthopedic surgeon explains:

"*…the guidelines state that the patient must be offered conservative treatment before surgery.*" (Orthopedic surgeon 1, single interview).

However, the decision of treatment is more complex than simply referring all patients without preceding non-surgical treatment to e.g. exercise therapy. The clinical experience and expertise of the orthopedic surgeons and patient preferences also affect the treatment decision.

Sub-theme 4: Must believe in exercise as treatment for patients with severe knee OA

Despite the guideline recommendations, it is the general opinion among the interviewed orthopedic surgeons that some patients should not try out exercise treatment but should be offered surgery right away because of the severity of their symptoms, associated x-ray and lack of effect of e.g. analgesic treatment. The orthopedic surgeons state that it would be a waste of resources to do anything else than offer surgery, because they believe that no other treatment is effective enough in relieving the patient's symptoms. If a patient with severe symptoms is referred to exercise treatment, the orthopedic surgeons are convinced that the patient will come back without feeling better. One orthopedic surgeon gave an example:

"If, you have a patient, let's say, an 80-year-old male with a really bad varus-knee with bone-on-bone in all three compartments and receiving strong pain medication. Then sometimes you might think, "it is really stupid to refer him to exercise for three months" because it would be a waste of time." (Orthopedic surgeon 1, single interview).

Referring patients to exercise challenges the orthopedic surgeon's professional role and self-image, as it becomes ambivalent to refer patients to exercise, as the guidelines recommend, when they doubt the effectiveness of the treatment. This was evidenced in statements like the one below:

"*Well, for me as a professional, we must at least believe a little in its (exercise) effectiveness before we refer patients to it, when we have the other alternative (surgery).*" (Orthopedic surgeon 2, single interview).

This opinion of offering surgical treatment initially without preceding (non-effective) non-surgical treatment is not the general view on exercise among the orthopedic surgeons. Only in patients with very strong, long-lasting symptoms. The decision to refer patients for exercise treatment is easy when the orthopedic surgeon does not believe that surgical treatment is warranted, that is, in patients with mild-to-moderate OA. One orthopedic surgeon explained:

"*Patients with knee pain, mild to moderate osteoarthritis, who haven't tried conservative treatment are eligible for exercise.*" (Orthopedic surgeon 3, single interview).

If symptoms progress, surgical treatment might be needed (8). Generally, when assessing the indication for surgery, the orthopedic surgeons agree that knowledge about the effect of exercise treatment provides clinically-relevant information aiding the decision to proceed with surgery or not. One situation discussed by the orthopedic surgeons was that if exercise treatment improves symptoms, then surgery might not (yet) be warranted. Contrary, lack of treatment effect from exercise could strengthen the argument for surgical treatment. One orthopedic surgeon stated:

"*I can certainly tell you this. If the patient's symptoms are unchanged and they are still in so much pain that the indication for surgery is there, then there is no doubt that surgery is the right treatment. If they have had no effect from exercise.*" (Orthopedic surgeon 3, single interview).

Sub-theme 5: Patient preferences

A number of points made by the orthopedic surgeons demonstrate the complexity of referring patients to exercise therapy. Patient characteristics can also play a role. The orthopedic surgeons expressed concern in referring older patients with no history of exercising to an exercise intervention, as they were unsure if the patients would adhere or be motivated. This was shown in statements like the following:

"*Well, some of them are not used to exercise. There are a lot of patients in this age-group who are not used to exercise. They have never done it. Nowadays plenty of people exercise, also in their 40's and 50's. But in that generation now in their 60's, many of them have never exercised. I think this makes it more difficult for them, mentally.*" (Orthopedic surgeon 3, single interview).

The orthopedic surgeons also expressed concern for patients still active in the labor market who do not want a prolonged treatment (e.g. because of pressure from their employer or the risk of losing their job). The orthopedic surgeons could be inclined to suggest surgery as they see this as the treatment with the most certain course (time, effect, risks). On the contrary, the effect of exercise is smaller than that of surgery in most cases and the possibility of a positive treatment outcome more uncertain. This suggests that a patient who is still active in the labor market could be offered surgical treatment regardless of prior non-surgical treatment. An orthopedic surgeon explains:

"*If you take a hard look at it, with a patient whose job is at risk and who needs to return quickly to the labor market, then it nevertheless plays a role for him, whether you choose a treatment with a success rate of 80-90%, which is a "high risk, high reward" treatment (surgery), or you choose to postpone surgery for three months with a treatment (exercise) that might or might not be effective with a lower success rate, with no complications. If you are retired, you are more likely to say: "I would like to try (exercise) because I'm not worried". But if you know you will be fired then it is another matter and you would like the operation here and now.*" (Orthopedic surgeon 1, single interview).

Another example was that of patients who are not motivated for treatment with a more unsure outcome and possibly extended overall treatment time. One orthopedic surgeon said:

"*Most of the patients not motivated for exercise are those still active in the labor market who need to return to their job and thus need a quicker solution.*" (Orthopedic surgeon 1, single interview).

Regardless of any treatment, surgical or non-surgical, a fundamental criterion for treatment success is the patient's motivation for the treatment. Generally, motivation seems to transcend all characteristics that might affect the treatment of choice, making it a relevant point in all patients. One orthopedic surgeon explains:

"*It is a question of whether the patients actually do it (exercise). How compliant they are. Because, you can easily send the patients home and say they should exercise. The question is, however, whether they actually do it. That is the problem*" (Orthopedic surgeon 3, single interview).

Thus, motivation is an important patient characteristic for the orthopedic surgeons, as they do not want to refer patients to a treatment that they are not going to adhere to due to lack of motivation. This would be a waste of everyone's time and resources.

Theme 2: Orthopedic surgeons' view on exercise

Among the interviewed orthopedic surgeons there is a variation in the views and opinions regarding exercise and the applicability of this in patients with severe knee OA. This variation could influence the treatment offered to patients depending on which orthopedic surgeon they consult.

Sub-theme 1: Skepticism towards (long-term) effect of exercise

The orthopedic surgeons consider exercise to be an integrated part of the treatment options they use in their clinical work. Exercise is widely accepted as a treatment option in patients with mild to moderate knee OA. However, there is considerable skepticism among orthopedic surgeons towards exercise as a treatment modality for patients with severe knee OA. The main skepticism is related to a lack of belief in the effectiveness of this treatment. One orthopedic surgeon stated:

"*Well, no, I am a little in doubt of how effective it (exercise) is. Patients on painkillers with a lot of pain who clearly have arthritis and that type of thing, I don't really believe that any of them can avoid surgery.*" (Orthopedic surgeon 2, single interview).

This skepticism is greater when it comes to long-term effects of exercise. The orthopedic surgeons know that surgery is very effective (when successful) in the long-term. On the contrary, exercise, if effective at all, is only effective when maintained. The following excerpt illustrates the orthopedic surgeon's attitude towards this:

"*I question whether it is at all fair (to refer patients with severe knee OA to exercise). I think of this when they (the patients) have a lot of discomfort and pain and osteoarthritis and you know it helps a lot of patients with knee arthroplasty. I also think it might well be that exercise helps, but I seriously doubt that the effect will be long-term. I don't have anything to base this on, but ....*" (Orthopedic surgeon 2, single interview).

Further, the orthopedic surgeons are skeptical towards patient adherence to exercise. An orthopedic surgeon can easily refer a patient to exercise if he/she deems this to be the best treatment option at the time. However, referring a patient to exercise does not mean that the patient complies with this, potentially making the referral a waste of time. This focus on patient adherence to prescribed exercise harmonizes well with the physical therapists' emphasis on adherence. An orthopedic surgeon explains:

"*But there are some patients who say, "I don't want to exercise". That is, "I have heard about it and I don't want to exercise, I would like an operation". You can take the horse to water, but you can't make it drink [provided as an analogy]. It might be that I refer the patient to exercise and that I insist on it. But if the patient comes back three months later and says, "I have not been exercising, now I would like an operation", then the recommendations have been met, but you have wasted three months of both his and my time.*" (Orthopedic surgeon 1, single interview).

Lack of belief in the effectiveness of exercise, doubt about the long-term effects of exercise and uncertainty about patient's adherence to exercise create skepticism in the orthopedic surgeons, and these become barriers to referring patients to exercise.

Sub-theme 2: Different purposes of referring a patient to exercise

The single interviews showed that there is large variation in how exercise is used as a treatment modality among the orthopedic surgeons. Some of the orthopedic surgeons use exercise therapy as a treatment and assess the result on knee-related symptoms, while others use exercise therapy as a means of assessing patient resources and motivation for exercise or to provide them with a "breathing space", where they can consider the possibility of surgery. This was evident form statements like this:

"…when you get the impression that the patient is not completely aware of what it (surgery) involves, then exercise provides a breathing space and it might also help…" (Orthopedic surgeon 1, single interview).

Also, a patient who is not adhering to exercise prior to surgery, could have difficulties completing the necessary rehabilitation following surgery. This could make the orthopedic surgeon reconsider the decision of whether surgery is the right treatment for the patient. At the same time, exercise therapy is a "safe" treatment (low risk of complications) that could reduce symptoms, and at the same time the patient is not rushed into a decision about surgery. One orthopedic surgeon explains:

"*So, for me it (exercise) is also a means to see if we should use surgery. But sometimes it is just as much a means to evaluate their motivation. Because if they don't want to exercise at all then their expectations following the operation must be re-assessed. So, I also use it (exercise) as an analysis of their personality. Also, in relation to exercise following surgery.*" (Orthopedic surgeon 4, single interview).

Another view on exercise is that it is a treatment where the patient "can be parked" until surgery is needed. From this perspective, exercise is used in a less constructive and inclusive way, and more as a practical solution that can be used until the patient is ready for surgical treatment. One orthopedic surgeon explained:

"*It (exercise) can be an advantage. If I don't think they are candidates for surgery, then I "park" them out there (to exercise).*" (Orthopedic surgeon 3, single interview).

A general point made by all the orthopedic surgeons is that exercise comes with a low risk of complications and is therefore worth trying when there is uncertainty concerning whether to proceed with surgery. The citation below illustrates this:

"*It is worth a try to postpone surgery three months and try exercise. It might help, and it might not…It also worth a try if you can avoid surgery and the associated complications.*" (Orthopedic surgeon 1, single interview).

Assessing the effect of exercise on knee-related symptoms, evaluating patient resources, and providing patients with a "breathing space" to consider the treatment option of surgery all become facilitators for referring a patient to exercise.

Essentially, the orthopedic surgeons act as gate-keepers for the different treatment options. The decision of whether patients eligible for KR are referred to exercise prior to potential surgery relies heavily on the preferences of the orthopedic surgeon. An orthopedic surgeon stated:

"*That is probably the biggest influence we have. To select the patients.*" (Orthopedic surgeon 1, single interview).

In summary, results from our single interviews with the orthopedic surgeons show that adhering to clinical guideline recommendations - and at the same time using clinical expertise and considering patient preferences - creates a professional dilemma among the orthopedic surgeons. On the one hand, facilitators such as *using exercise as a means to examine patient's motivation for rehabilitation*, *providing patients with a low-risk-of-complications treatment while considering the option of surgery* and *knowledge of the effect of exercise can help guide the decision of surgery* support the use of exercise as a treatment modality among orthopedic surgeons for patients with severe knee OA. On the other hand, barriers among the orthopedic surgeons towards referring patients with severe knee OA to exercise were *skepticism towards the effect of exercise and especially the long-term effect in patients with severe knee OA* and *the dilemma of referring patients to exercise who are not motivated for this treatment modality*. These barriers challenge the orthopedic surgeons creating ambivalence in their professional role.

Theme 3: Coordinated non-surgical and surgical care

Orthopedic surgeons and physical therapists are preoccupied with different aspects of coordinated non-surgical and surgical care. The orthopedic surgeons focus on what kind of treatment they refer to, while the physical therapists focus more on the care pathway as a whole.

Sub-theme 1: Orthopedic surgeons' skepticism to the content of the exercise treatment they refer to

A general skepticism concerning referring patients to exercise is that the orthopedic surgeons experience a large variation in the type of exercise intervention the patients are offered following referral. An orthopedic surgeon explains:

"*But you hear a lot of different things. Some have had very good exercise treatment while others have had massage for three months, which might be nice, but I doubt that it helps with their osteoarthritis symptoms.*" (Orthopedic surgeon 1, single interview).

Another barrier to referring patients to exercise is the time required to inform patients about exercise. An orthopedic surgeon says:

"*But there's a lot of information in this (referral to exercise). It is a lot easier to schedule the patients for surgery. It requires a lot more to information to send them (the patients) to training.*" (Orthopedic surgeon 4, single interview).

An advantage of referring patients to the QUADX-1 exercise intervention is that the orthopedic surgeons know exactly what the intervention comprises. An orthopedic surgeon explains:

"*The advantage of this (the QUADX-1 intervention) is that you know what you get. We cannot refer directly to other exercise treatments where we know the content.*" (Orthopedic surgeon 1, single interview).

Sub-theme 2: Responsibilities in coordinated care and engagement in the care pathway

When an orthopedic surgeon refers a patient to non-surgical treatment then "the surgeon's work is done". All practicalities related to coordinating treatment across sectors should be managed by secretaries, according to the orthopedic surgeons. An orthopedic surgeon says:

"*Well, I just assess the patient and refer them to exercise and they get a new appointment three months later. Then I don't do anything more.*" (Orthopedic surgeon 3, single interview).

And

"*The secretary has to keep track of it (the referral to exercise in the municipality). I should do as little as possible in that respect.*" (Orthopedic surgeon 3, single interview).

Once an orthopedic surgeon has referred a patient to exercise then the physical therapist has responsibility for the treatment. An orthopedic surgeon explains:

"*In principle it is the responsibility of the physical therapist that the exercise intervention is completed*." (Orthopedic surgeon 3, single interview).

The physical therapists are positive towards coordinated non-surgical and surgical treatment as they believe the patients are provided with an altogether better care pathway when exercise is tried before the decision for surgery is made. This was shown in statements like the following:

"*I like the idea - that the patient isn't told at the first consultation that "you need a knee replacement" – that exercise is tried and then the need for surgery is re-evaluated. That is, "this (exercise) worked for me", or "this did not work for me". I think this is a reasonable care pathway.*" (Physical therapist 4, focus group interview).

The physical therapists also believe that patients would appreciate such a coordinated care pathway and would feel confident that all treatment options have been explored. Further, in such a coordinated care setting the patients would experience that the health care professionals at the hospital and in the municipality are communicating and working together. A physical therapist explains:

"*...I think that the individual patient will feel that they have been taken good care of... That all treatment options have been tried out and that they have had a good care pathway... Also, in relation to communication, that they (the patients) experience that we and they (the orthopedic surgeons at the hospital) are 'on the beat'. That it is a transparent care pathway.*" (Physical therapist 6, focus group interview).

The physical therapists see another advantage of the coordinated care. Patients that postpone surgery and continue with exercise can be helped in the municipality to maintain their exercise program and can be guided to local gyms and other activities. A physical therapist explains:

"*If all care and treatment took place at the hospital, then it could be even more difficult (for the patients) to continue (to exercise) in a local gym... The municipalities are less institutionalized compared to hospitals, and we have better knowledge of the local exercise options. I think this is an advantage.*" (Physical therapist 2, focus group interview).

In summary, the orthopedic surgeons express frustration with variation in the treatment provided for the patients when they refer them to exercise in the municipality which becomes a barrier to referring patients to exercise. The physical therapists are positive in respect of the coordinated care pathway as they believe this will mean that patients are provided with quality care. This becomes a facilitator for coordinated non-surgical and surgical treatment.

Discussion

This study applied a thematic analysis to identify facilitators and barriers among orthopedic surgeons and physical therapists towards a coordinated care pathway of non-surgical and surgical treatment of severe knee osteoarthritis using pre-operative home-based exercise with *one* exercise. Three interrelated themes were found important for whether coordinated surgical and non-surgical care of home-based exercise therapy with *one* exercise was perceived as a facilitator or barrier: 1) Physical therapists and orthopedic surgeons' ambivalence in their professional roles, 2) Orthopedic surgeons' view on exercise, and 3) Coordinated non-surgical and surgical care. How coordinated non-surgical and surgical care with home-based exercise therapy with *one* exercise challenges both professions and create ambivalence in their professional roles will be discussed first. Then the orthopedic surgeons' view on exercise and finally the two professions different focus in coordinated non-surgical and surgical care will be discussed.

For the physical therapists, exercise therapy is a central treatment modality characterizing their profession (10,12). Traditionally, exercise therapy is provided at supervised group sessions allowing physical therapists to monitor treatment closely and adjust accordingly. Reimbursement or self-payment of lifelong supervised exercise is not realistic for most patients making self-management critical. The Osteoarthritis Research Society International (OARSI) recommend patient self-management in their guidelines for non-surgical treatment of patients with knee OA (7). Providing patients with tools for self-management enables patients to adjust home-based exercise and activities of daily living accordingly (knee pain and symptoms) thereby increasing the chance of maintained successful treatment (40,41). The physical therapists interviewed in the present study recognize the importance of providing patients with tools to self-manage their condition and acknowledge the benefits of home-based exercise therapy. Interestingly, this aspect of educating patients in self-management is to some degree in conflict with the physical therapists' engaged treatment approach and strong physical therapist-patient relationship. Through self-management education, physical therapists educate patients to manage their condition without supervision from a physical therapist, making themselves expendable. Their acceptance could be explained by their professional role and the concomitant ethical responsibility to do what is best for the patient (10). This acknowledgement of supporting self-management in patients becomes a facilitator for potential clinical implementation of the simplified treatment approach.

Both professions are educated to become autonomous professional practitioners (10,12,42). The sociologist Wilensky defines (healthcare) professionals as: *professionals make inferences; they treat individual clients, make specific decisions, analyze specific cases, or give specific advice on the basis of learned, abstract insights* (43), meaning that a professional has acquired standardized skills enabling them to apply knowledge and treat cases (e.g. patients) (44). Without this premise, anyone could perform professional work (43). With this perspective, it is understandable why the physical therapists experience home-based exercise therapy with *one* exercise as a challenge to their professional role. Their normal practice consists of going from a lot of supervision and guidance towards less, as the patients become more independent. Even though the physical therapists distance themselves from the patients, they keep some control over the patient's treatment (13,14). In the single exercise model, this practice is replaced with only one supervised session after which the patient alone is responsible for the exercise therapy. Home-based exercise therapy with *one* exercise limits the physical therapists' possibility to advise and adjust treatment along the way, which means that they do not have the same control over the treatment as usual. The experience of loss of control challenges their profession role and becomes a barrier for implementing home-based exercise therapy with *one* exercise.

"The modern professional role" as described by Abbott (45) further supports the physical therapists' skepticism towards a less engaged and simplified professional role and treatment approach. Abbott views professions as knowledge systems and describes professional work in three parts: 1) classification of problems combined with information on the specific case and professional expertise, 2) translation of professional expertise to potential solutions for the individual case and 3) to reason and specify the solution into one treatment. In the profession of physical therapy, the first part is comparable to information from a patient's medical history, which is supplemented with a clinical examination, while the second and third part overlap in the process of clinical reasoning and treatment (10,12). In this perspective, a simplified treatment approach could limit physical therapists´ use of their professional knowledge and expertise. This challenges the physical therapists, as it confronts their professional skills, clinical reflection and reasoning, which become less important as the treatment has been defined beforehand by others (10). This is in line with previously reported barriers among physical therapists towards home-based exercise therapy with *one* exercise, i.e. “too simplistic” and “restricted intervention, wanted to add manual therapy as a treatment option” and “the role of on-going support” (21).

When an orthopedic surgeon considers surgery for knee OA for a patient who has *not* tried exercise therapy, has strong knee OA symptoms and meets the clinical indication for surgery (i.e. state of the joint, pain and functional disability), then the orthopedic surgeons’ professional role is challenged. According to clinical guidelines (7,8), the patient should be referred to exercise therapy to see if this treatment is effective in reducing symptoms. This could conflict with the orthopedic surgeon’s opinion of what would be the right treatment, for example due to a skepticism towards the long-term effectiveness of exercise. The orthopedic surgeon could argue that surgery should be offered right away since the indication for surgery is met regardless of whether the patient has tried non-surgical treatment or not. In this situation, the preferences of the orthopedic surgeon become a barrier for adherence to clinical guidelines (including referral to exercise therapy).

Other challenges for the orthopedic surgeons are their role as agents for the healthcare system. An agent is understood as “one who chooses as the patients themselves would choose if they possessed the information that the orthopedic surgeon does” (46). Orthopedic surgeons are specialists in orthopedic surgery, and on the one hand they must adhere to clinical guideline recommendations of, for example, exercise therapy. On the other hand, they have to offer the treatment they professionally believe is the correct treatment for that patient at that time (fulfills patient preferences), for example, surgery. Orthopedic surgeons are members of the medical profession, operating under the ‘medical pledge’, and are thus primarily taking care of the patient’s preferences rather than what clinical guidelines prescribe (The World Medical Association, Inc, 2005). Thereby, they appear not only to be agents but to be double agents. That is, they are obliged to follow clinical guideline recommendations and at the same time take the patient’s preferences into account while also using their clinical expertise. Further, they also need to ensure that a certain number of patients are referred to surgery as the department is economically dependent on the number of surgeries completed. This double agent position can become a barrier for referring patients to exercise therapy. These barriers may not only be relevant for the present study. They may provide new targets for future implementation studies of current guidelines concerning the non-surgical treatment of patients considered for surgery in general.

Another central finding from the study is how orthopedic surgeons expressed skepticism towards (long-term) effect of exercise as a treatment modality in patients with severe knee OA. This skepticism becomes a barrier for referring patients to exercise therapy and a facilitator for referring patients directly to surgery. This finding is supported by data from a study where, if an orthopedic surgeon had a "lack of belief in physical therapy when there is an obvious loss of cartilage" this was associated with fewer referrals to physical therapy (15). Some orthopedic surgeons question the long-term effect of exercise therapy, which may relate to how they are used to thinking about intervention and effect, that is, they are used to long-lasting effects of their single intervention (surgery). A one-time intervention with exercise therapy (one single session) will have no long-lasting effect without being supplemented with more sessions (47,48). This is no different from administering a single dose of insulin to a diabetic, where a long-lasting effect is not expected unless supplemented with further doses of insulin (49). What also makes the insulin-analogy relevant is that the intervention requires behavioral changes in patients, which is also the case for patients with knee OA, who do not necessarily exercise regularly (50). Taken together, different professions may have different opinions and understandings of the short- and long-term effects of the different interventions that they use to treat patients.

Despite skepticism towards the effect of exercise, the orthopedic surgeons recognize the value of exercise as a treatment modality in their clinical work. For patients in doubt of whether to undergo surgery, a less invasive treatment option is welcomed while the patients consider the option of surgery and associated risks. This recognition of exercise as an option to provide patients with a non-invasive treatment while considering surgery and as a means to supplement the indication for surgery becomes a facilitator for referring patients to exercise.

The recognition of exercise among the orthopedic surgeons also relates to different considerations when referring patients to exercise. Social support and health beliefs besides disease severity are important in the decision of which treatment to proceed with (42). Gossec et al. found that severity of pain and functional disability could not distinguish between those who were or were not recommended for KR in patients with radiographically verified hip or knee OA (51). Similarly, Skou et al. found similar pain levels in patients deemed eligible and not eligible for KR (52). The decision concerning referral to exercise relies heavily on the preferences of the orthopedic surgeon, that is, whether exercise is used to assess the treatment effect on knee OA-related symptoms, assessing patient resources and motivation, or as a “breathing space” where the patient can consider the possibility of surgery. Referral practice among orthopedic surgeons has previously been reported to vary depending on the level of professional experience (53). Essentially, the orthopedic surgeons act as gate-keepers for the different treatment options, and this role as gate-keeper becomes both a facilitator and a barrier depending on the purpose for referring or not referring patients to exercise.

In respect of the coordinated care, the main barrier expressed by the orthopedic surgeons was the variation in treatment received by patients in the municipality, as previously reported (15). An advantage of the QUADX-1 intervention for the orthopedic surgeons was that they knew what the content of the exercise intervention was. In relation to the coordinated care pathway the orthopedic surgeons mainly focus on their own role, e.g. scheduling patients for surgery or referring to non-surgical care. Conversely, the physical therapists focus more on the care pathway as a whole. It becomes a facilitator for the physical therapists to contribute to the coordinated care pathway by providing exercise before the decision on surgery is taken. Optimized coordination of non-surgical and surgical care provides patients with a more comprehensive care pathway exhausting non-surgical treatment options before potential surgery. This may change the care pathway for some patients with postponed surgery, while shortening surgical waiting time for other patients in greater need of surgical care.

In summary, the model of coordinated non-surgical (home-based exercise therapy with *one* exercise) and surgical treatment challenges both the physical therapists and the orthopedic surgeons and creates an ambivalence in their professional roles in different ways. This ambivalence causes mixed feelings and sometimes conflicting interest in the two professions about how to handle home-based exercise therapy with *one* exercise as evidenced by the different facilitators and barriers in the two professions. Thus, even though home-based exercise therapy with *one* exercise is described and discussed as a standardized and practically simple intervention (24) the results from the study show that the intervention is perceived as complex in the context of clinical interprofessional coordination of treatment (54,55). The intervention is assigned a situated meaning from the two professions and is not a uniform object shown by the different facilitators and barriers. This is important knowledge for future implementation of the intervention, where it is not uncommon to think of the implementation as standardized leading to a "one size fits all" implementation approach. When implementing the intervention, it must be considered “complex”, where several implementation strategies must be used (a multifaceted approach) (56). Further, the intervention must be adapted to both professions, that is, the situated meaning and the facilitators and barriers the physical therapists and orthopedic surgeons experience.

Strengths and limitations

This study has both strengths and limitations which should be considered when interpreting the findings. One of the main strengths is that all potential participants were included for the interviews. That is, all physical therapists and eligible orthopedic surgeons (supervisors and co-authors deemed not eligible due to conflict of interest) involved in the QUADX-1 trial participated in the interviews. Further, the study involves both groups of healthcare professionals that coordinate treatment for patients with severe knee OA in their daily clinical practice (i.e. physical therapists and orthopedic surgeons). The study is reported according to the Standards for Reporting Qualitative Research: A Synthesis of Recommendations (SRQR) checklist (57), which we believe strengthens the transparency and validity of the study.

The main limitations are that despite including all potential participants for the interviews, we only interviewed six physical therapists and four orthopedic surgeons. It is unknown if additional participants would have added new perspectives or further supported the findings of the study, that is, a higher degree of data saturation. The use of two different interview approaches (focus group- and single interviews) could have introduced bias. By only applying single interviews for the orthopedic surgeons, we missed the interactions created during focus group interviews. Conversely, in single interviews the participant is not at risk of being overwhelmed or ignored by more dominant participants. Though interview data from the orthopedic surgeons was collected on an individual basis the same themes were present among the interviewed orthopedic surgeons (34). The primary investigator's (RSH) professional background is physical therapy. His preconception of both the physical therapy and orthopedic surgery professions could have affected his conducting of interviews, data analysis and interpretation of the results. To accommodate this, all steps were discussed with and approved by co-authors (TB and JK) during the process and the final results were approved by all co-authors (i.e. physical therapists, an orthopedic surgeon and a nurse).

Conclusion

We found that both physical therapists and orthopedic surgeons were challenged by coordinated non-surgical and surgical treatment of patients with severe knee osteoarthritis using pre-operative home-based exercise therapy with *one* exercise as evidenced by the identified facilitators and barriers. The intervention created ambivalence in the professional role of both the physical therapists and orthopedic surgeons. The physical therapists were skeptical about over-simplified exercise therapy but positive towards patient self-management. The orthopedic surgeons were skeptical about the potential lack of a long-term effect of exercise therapy in patients with severe knee OA but acknowledged exercise therapy as an alternative treatment option in daily clinical practice. This ambivalence in the professional role is important to consider when planning implementation of the intervention as it may appear simple but is regarded as complex.

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Supporting information captions

S1 Appendix 1 – SRQR Checklist

S2 Appendix 2 - Interview guide physiotherapists

S3 Appendix 3 - Interview guide orthopedic surgeons

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Standards for Reporting Qualitative Research (SRQR)*
http://www.equator-network.org/reporting-guidelines/srqr/

Title and abstract

	Page/line no(s).
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	4-6
Purpose or research question - Purpose of the study and specific objectives or questions	6

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	6-12
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	8
Context - Setting/site and salient contextual factors; rationale**	6
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	7-9
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	12
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings;	8-10

rationale**	
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	10-11
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	8-9
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	10-11
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	10-11
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	10-11

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	11-26
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	11-26

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	12-32
Limitations - Trustworthiness and limitations of findings	39-40

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	Appendix
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Appendix

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.**
Academic Medicine, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

Interview guide physiotherapists

Therapist information

Age
Municipality

1. **The role of the physiotherapist in this type of exercise therapy intervention (exercise instruction followed by home-based exercise)**
    a. What kind of role do you think you will have in this type of physiotherapy?
        i. Advantages, disadvantages or possibilities?
    b. Reflect on how this home-based/self-management approach is different from your current treatment of these patients.
        i. Advantages, disadvantages or possibilities? Time?

    <u>Supplementary questions if topics not discussed from the above</u>
    c. Do you experience that you lose professionalism when instructing patients and send them home compared to supervising their treatment (exercise) and the quality of the treatment?
        i. Advantages and/or disadvantages of this un-supervised type of physiotherapy?
    d. Can more time by allocated to patients with higher need when patients with knee osteoarthritis exercise at home?
    e. Does this approach change your role in relation to motivating patients to exercise?
        i. E.g. adherence to home-based exercise/"sell the idea" (pedagogy)?
        ii. Does this role acquire other skills from you? If so, which?

2. **Pre-operative exercise**
    a. Which possibilities or barriers do you see in relation to exercise therapy in patients with end-stage knee osteoarthritis?
        i. Advantages and disadvantages for both physiotherapists and patients?

3. **Non-supervised exercise therapy**
    a. Which possibilities and barriers do you see in relation to non-supervised exercise therapy?
        i. Advantages, disadvantages why?
    b. To what extent do you think that the patients can get the same quality in the exercise therapy when you are not there to supervise them?
        i. Why, why not?

    <u>Supplementary questions if topics not discussed from the above</u>
    c. Are the patients able to adhere to the pre-scribed exercise dosage when not supervised? Why, why not? Elaborate.
    d. Are the patients able to exercise with the same quality non-supervised as supervised?
        i. Why, why not? Elaborate.

4. **One-exercise exercise therapy**
    a. Reflect on the rehabilitation approach with *one* exercise. How does this deviate you're your current practice?
        i. Advantages, disadvantages to this approach?
    b. Reflect on the effect of exercise therapy with *one* exercise. What does it require to achieve effect?

        i. Why?
    c. What do you think the patient's thoughts are on this?
        i. Why?

5. The model of coordinated non-surgical and surgical treatment

a. What are your thoughts on the model where the coordination between municipality and hospital is initiated before potential surgery?
    i. Which advantages, disadvantages or possibilities do you see in the model? Both to yourselves and for the patients?
b. Is the model of coordinated non-surgical and surgical treatment applicable to your daily clinical practice?
    i. If not, what would need to be changed for it to be applied?
c. What are your thoughts on the model of coordinated non-surgical and surgical treatment on an organizational level?
    i. Advantages, disadvantages or possibilities? Is it implementable?

6. Other

a. Topics we have not discussed which you would like to comment on?

Interview guide orthopedic surgeons

Surgeon information

Age

1. **The model of coordinated non-surgical and surgical treatment prior to surgery**
    a. What are your thoughts on referring candidates for total knee arthroplasty to non-surgical treatment in the form of exercise therapy prior to potential surgery (the model)?
        i. Which advantages, disadvantages or possibilities do you see in this coordination of non-surgical and surgical treatment? Both to yourself and to the patients.
    b. Can this coordination of non-surgical and surgical treatment (the model) be adapted to your clinical practice?
        i. If not, what should be changed for it to be adapted?
    c. What are your thoughts on the coordination of non-surgical and surgical treatment (the model) on an organizational level, that is, who is responsible for running it?
    d. Advantages, disadvantages or possibilities? Can it (the model) be implemented?
    e. What do you consider the most important factor we should aware of in this project?

2. **The role of orthopedic surgeons in the pre-operative coordination of non-surgical and surgical treatment**
    a. What role do you think you as orthopedic surgeons will have in this coordination of non-surgical and surgical treatment?
        i. Advantages, disadvantages or possibilities?
    b. What type of patients (characteristics) do you consider good candidates to try exercise therapy prior surgery?
        i. Why, why not?
    c. Are there patients whom you do not think will benefit from exercise therapy but who should undergo surgery right away?
        i. Why, why not?
    d. Which barriers do you see in relation to systematically using exercise therapy in the treatment of patients with knee osteoarthritis?

3. **Re-evaluation of the most optimal treatment on a better basis (shared decision making)**
    a. The purpose of the project is that the evaluation of the most optimal treatment for the patient is based on the best possible basis, that is, that non-surgical treatment has been tried prior to surgery. Do you think this will provide you with a more optimal basis in relation to whether surgery is the best treatment or not?
        i. Why, why not? Advantages, disadvantages or possibilities?
        ii. What do you think the patients' thoughts are on this?

4. **Self-management**
    a. As part of the non-surgical treatment the patients also receive tools (self-managed exercise therapy and pain management) to manage their knee related symptoms? What are your thoughts on this education of the patients to better self-manage their condition?
        i. Advantages, disadvantages or possibilities?

5. **Potentially better rehabilitation**

a. If the exercise therapy is effective some patients might postpone their surgery, while those who undergo surgery likely will have an easier rehabilitation. What are your thoughts on these two scenarios? i. Advantages, disadvantages or possibilities?
6. Other a. Topics we have not discussed which you would like to comment on?