SDU
Syddansk Universitet

Department of Clinical Research

PhD Thesis

Thomas Frydendal

SURGICAL AND NON-SURGICAL TREATMENT IN THE MANAGEMENT OF HIP OSTEOARTHRITIS

Total Hip Arthroplasty versus Progressive Resistance Training in Patients with Severe Hip Osteoarthritis (The PROHIP Trial)

May 2023

Supervisors

Principal supervisor

Robin Christensen, Professor, PhD

[1] Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark

[2] Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

Co-supervisors

Kim Gordon Ingwersen, Associate Professor, PhD, PT

[1] Department of Physio- and Occupational Therapy, Lillebaelt Hospital – University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark

[2] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

Inger Mechlenburg, Professor, DMSc, PhD, PT

[1] Department of Orthopaedic Surgery, Aarhus University Hospital, Aarhus, Denmark

[2] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Lone Ramer Mikkelsen, Associate Professor, PhD, PT

[1] Elective Surgery Centre, Silkeborg Regional Hospital, Silkeborg, Denmark

[2] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Søren Overgaard, Professor, DMSc, PhD, MD

[1] Department of Orthopaedic Surgery and Traumatology, Copenhagen University Hospital, Bispebjerg Hospital, Copenhagen, Denmark
[2] Department of Clinical Medicine, Faculty of Health and Medical Sciences University of Copenhagen, Copenhagen, Denmark

Committee Members

Chair

Jan Hartvigsen, Professor, PhD

[1] Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

[2] Chiropractic Knowledge Hub, Odense, Denmark

Members from other institutions

Eva Ageberg, Professor, PhD, PT

[1] Department of Health Sciences, Lund University, Lund, Sweden

Rudolf Poolman, Professor, PhD, MD

[1] Department of Orthopaedic Surgery, Joint Research, OLGV, Amsterdam, the Netherlands

[2] Department of Orthopaedic Surgery, Leiden University Medical Center, LUMC, Leiden, the Netherlands

Preface

The studies presented in this PhD thesis were conducted during my employment as a PhD fellow at the Department of Physio- and Occupational Therapy, Lillebaelt Hospital – University Hospital of Southern Denmark, Vejle Hospital and Department of Clinical Research, University of Southern Denmark (2018-2023), under main supervision of Professor Robin Christensen focusing on the clinical epidemiology related to surgical and non-surgical treatment for hip osteoarthritis. Figure 1, 3, 4, 5, 6, 7, 8, 13, and 15 in this PhD thesis have been developed with the use of images or vectors from Colourbox.com. Any reuse of figures or tables from the papers or manuscripts, in which this PhD thesis is based upon are clearly highlighted.

Acknowledgements

I am thankful to have collaborated with several highly competent people who have supervised and motivated me during the past five years, and provided me the opportunity of combining clinical work with an academic career as a researcher determined to improve the treatment of hip osteoarthritis.

First, I would like to acknowledge my main supervisor Professor Robin Christensen, a biostatistician with great expertise and state-of-art knowledge about designing, analysing, and reporting of high quality prospective research, including randomised trial designs. I have enjoyed your straightforward nature and support during our collaboration.

Second, I also would like to send a huge acknowledgement to all of my co-supervisors: Assistant Professor Kim Gordon Ingwersen for highly valued and extraordinary support on a daily basis and sharing knowledge about running a multicentre randomised trial; Professor Inger Mechlenburg for facilitating great collaborations with other research environments and being an inspirational key figure who helped in expanding my professional academic network; Associate Professor Lone Ramer Mikkelsen for key inputs, constructive positive feedback, and clinical and physiological perspectives on progressive resistance training; and Professor Søren Overgaard for highly valuable inputs in general and specialised surgical insights related to total hip arthroplasty, as well as highlighting the importance of patient and public involvement in clinical research in order to improve a trial protocol.

Third, I also would like to thank all my colleagues at Vejle Hospital for making this period of my life unforgettable and allowing me to develop as both a clinician and researcher.

Fourth, I thank all my funders, The Danish Rheumatism Association, The Region of Southern Denmark, Region Zealand and Region of Southern Denmark joint research fund, The Association of Danish Physiotherapists Research Fund, The Research Council at Næstved-Slagelse-Ringsted Hospitals, and The A.P. Moeller Foundation for financing

this PhD project and the Odense Patient data Explorative Network (OPEN), Odense University Hospital for data management support and access to Research Electronic Data Capture (REDCap).

Fifth, I would like to acknowledge all the orthopaedic surgeons, local study coordinators, nurses, and physiotherapist who either were involved in the enrolment of patients or surgical treatment and postoperative rehabilitation, physiotherapists responsible for delivering and supervising the progressive resistance training, and the patients who agreed to participate in this project.

Sixth, I also thank all the outcome assessors for accurate testing of participants in the randomised trial at baseline and 6 months follow-up.

Finally, I want to express my sincerest gratefulness to my nearest family, especially my amazing girlfriend and our two wonderful little boys – your love and immense support provide meaning to my personal and professional life.

Thomas Frydendal, Physiotherapist, MSc

Thomas Frydendal

Abbreviations

30s-CST	30-seconds Chair Stand Test
40m-FPWT	40-meter Fast Paced Walk Test
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
CERT	Consensus on Exercise Reporting Template
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COREQ	Consolidated Criteria for Reporting Qualitative Research
COVID-19	Coronavirus Disease 2019
EQ-5D-5L	EuroQol Group 5-dimension 5-levels
EQ-VAS	EuroQol Group Visual Analogue Scale
HOOS	Hip disability and Osteoarthritis Outcome Score
IQR	Interquartile Range
MCII	Major Clinically Important Improvement
MIC	Minimal Important Change
MID	Minimal Important Difference
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
OA	Osteoarthritis
OHS	Oxford Hip Score

OARSI	Osteoarthritis Research Society International
OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
OPEN	Odense Patient data Explorative Network
OR	Odds ratio
PRT	Progressive Resistance Training
PROHIP	PROgressive resistance training versus total HIP arthroplasty
RD	Risk Difference
REDCap	Research Electronic Data Capture
RM	Repetition Maximum
SAEs	Serious Adverse Events
SE	Standard Error
SD	Standard Deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STDdiff	Standardised Difference
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
UCLA	University of California Los Angeles
VAS	Visual Analogue Scale

Table of Contents

Studies in this PhD thesis

This PhD thesis is based on the following papers or manuscripts of Study I to IV:

***Study I*. Patient and public involvement study**
Frydendal T, Thomsen KS, Mechlenburg I, Mikkelsen LR, Overgaard S, Ingwersen KG, Myburgh C. *Patient and Public Involvement to Inform The Protocol of a Clinical Trial Comparing Total Hip Arthroplasty With Exercise: An Explorative Qualitative Case Study*. BMJ Open 2023;13(4):e070866. doi: 10.1136/bmjopen-2022-070866.

***Study II*. Protocol for a randomised trial**
Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Overgaard S, Ingwersen KG. *Total Hip Arthroplasty versus Progressive Resistance Training in Patients with Severe Hip Osteoarthritis: Protocol for a Multicentre, Parallel-group, Randomised Controlled Superiority Trial*. BMJ Open 2021; 11: e051392. doi: 10.1136/bmjopen-2021-051392.

***Study III*. Cross-sectional comparison of self-reported baseline characteristics and outcome scores**
Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Varnum C, Bieder MJ, Jakobsen SS, Overgaard S, Ingwersen KG. *Different Self-reported Characteristics and Outcome Scores in a Randomized Trial Comparing Total Hip Arthroplasty with Exercise: A Cross-sectional Study of 402 Patients with Hip Osteoarthritis*. Manuscript (submitted, under review). May 2023.

***Study IV*. Primary and secondary outcomes from the randomised trial**
Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Varnum C, Graversen AE, Kjærsgaard-Andersen P, Revald PH, Hofbauer C, Bieder MJ, Qassim H, Munir MS, Jakobsen SS, Nielsen SM, Ingwersen KG, Overgaard S. *Total Hip Replacement or Progressive Resistance Training for Severe Hip Osteoarthritis*. Manuscript (not submitted yet). May 2023.

English Abstract

Introduction

Hip osteoarthritis (OA) is a major contributor to pain and functional impairments worldwide, with great financial costs for society. Hip OA affects around 1 out of 10, and it is the leading cause for total hip arthroplasty (THA). In individuals with severe hip OA, THA is considered an effective treatment to reduce pain, improve physical function, and increase quality of life, but the procedure is associated with a small risk of serious complications. On the contrary, progressive resistance training (PRT) is safe and appears to provide moderate improvements in pain, physical function, and quality of life even in individuals with severe hip OA. To date, THA has not been compared directly with PRT. This comparison is highly wanted as non-surgical treatment is considered as an alternative to surgery for many musculoskeletal disorders.

Aim and Objectives

The overall aim was to investigate the effectiveness of surgical and non-surgical treatment in individuals with severe hip OA considered eligible for THA. The specific study objectives were:

Study I. To explore patient, clinician, and decision maker stakeholders' perceptions on a randomised trial evaluating the effectiveness of THA compared with PRT to inform the development of the trial protocol.

Study II. To develop and describe a study protocol for a randomised trial comparing THA with a PRT program in individuals severe with hip OA.

Study III. To evaluate whether individuals with severe hip OA enrolled in a randomised trial comparing THA with PRT differed in self-reported characteristics and outcome scores from those who only accepted enrolment in a parallel prospective observational cohort at baseline.

Study IV. To investigate whether THA improved self-reported hip pain and function more than PRT in individuals with severe hip OA from baseline to 6 months follow-up.

Materials and Methods

Study I. Participants were enrolled into three key stakeholder groups: patients with severe hip OA considered eligible for THA, clinicians (orthopaedic surgeons and physiotherapist), and decision makers (politicians and non-governmental organisation representatives). Focus group interviews were conducted using open-ended semi-structured interview guides, according to group status. Interviews were recorded, transcribed verbatim, and thematic analysed using an inductive approach.

Study II. A protocol for a high quality, multicentre, parallel group, randomised controlled superiority trial comparing THA with PRT in individuals with hip OA was designed and described, including considerations about study design, inclusion and exclusion criteria, enrolment procedures, randomisation and allocation concealment, blinding, parallel observational cohort, interventions, outcomes, data collection, sample size and power calculation, and statistical methods.

Study III. Baseline data from the randomised trial (PROHIP) and parallel observational cohort (Non-PROHIP) was used. Participant characteristics and the Oxford Hip Score (OHS, range 0 [worst] to 48 [best], minimal important difference [MID]=5 points), the Hip disability and Osteoarthritis Outcome Score (HOOS) subscales (range 0 [worst] to 100 [best], MID=10 points), and University of California Los Angeles (UCLA) activity score (range 1 [inactive] to 10 [regular physical activity with high intensity], MID=2 points) were collected using electronic online questionnaires. Data were analysed using descriptive statistics, standardised differences, non-parametric tests, and univariate logistic regression.

Study IV. Participants were randomly assigned to receive either a THA followed by standard care or a 12 week supervised PRT program targeting lower extremity muscles performed twice a week followed by 12-weeks of optional non-supervised PRT. The primary outcome was the between-group difference in change in the OHS (range 0 [worst] to 48 [best], MID=5 points) from baseline to 6 months follow-up, analysed using a repeated-measures mixed effects linear model with adjustments for covariates.

Results

Study I. Four focus group interviews with a total of 14 patients, one focus group with 4 clinicians (2 orthopaedic surgeons and 2 physiotherapists), and one focus group with 4 decision makers (3 politicians and 1 non-governmental organisation representative) were conducted. Two main themes were developed. 'Treatment expectations and beliefs impact management choices' covered three sub-themes: Treatment without surgery is unlikely to lead to recovery; Clinician authority affects the management narrative; The 'surgery versus exercise' debate. 'Factors influencing clinical trial integrity and feasibility' highlighted three sub-themes: Who is considered eligible for surgery?; Facilitators and barriers for surgery and exercise in a clinical trial context; Improvements in hip pain and hip function are the most important outcomes.

Study II. The THA intervention consisted of a standard fast-track multimodal surgical program, which included patient information, optimised pain management, and early mobilisation. The surgical procedure was performed in accordance with the standard posterior approach, and postoperative rehabilitation followed hospital-specific procedures. The PRT programme comprised 10-min warm-up on stationary bicycle followed by four exercises performed unilaterally in machines or cable pulleys with full as full range-of-motion as possible in three sets separated by 60 seconds of rest. Progression of training load followed a linear model of periodization with an initial relative load of 12 repetition maximum (RM) in week 1-2, 10RM in week 3-6, and 8RM in week 7-12. Absolute training load was adjusted on set-by-set basis using muscular contraction to volitional failure and between sessions guided by hip pain.

Study III. In total, 402 participants were included in the analysis with 109 in PROHIP and 293 in Non-PROHIP. The PROHIP group had a better mean (±standard deviation) OHS (25.1±5.9 vs. 22.6±6.9, group difference 2.5 points [95% CI 1.1 to 4.0]) than the Non-PROHIP group. The PROHIP group also had better mean scores in all HOOS subscales (group differences were 4.9 points [95% CI 1.4 to 8.3] in HOOS pain; 5.6 points [95% CI 1.9 to 9.3] in HOOS symptoms; 7.4 points [95% CI 3.5 to 11.3] in HOOS function in

activities of daily living; 8.1 points [95% CI 4.0 to 12.2] in HOOS function in sport and recreation; and 7.7 points [95% CI 4.4 to 11.0] in HOOS quality-of-life), while there was no difference between the groups in the UCLA activity score (group difference 0.2 points [95% CI -0.2 to 0.6]). For the self-reported characteristics, the PROHIP group had a higher body mass index (group difference 1.4 kg/m2 [95% CI 0.5 to 2.3]) and a lower proportion had previously received THA (group difference -13.5% point [95% CI -20.9 to -6.0]), total knee arthroplasty (TKA) (group difference -6.4% point [95% CI -10.4 to -2.3]) or supervised exercise (group difference -10.8% point [95% CI -21.0 to -0.7]) compared with Non-PROHIP group.

Study IV. Among the 109 randomised participants (mean age, 67.6 years; 54 [49.5%] females), 103 (94.5%) completed the randomised trial. At the 6 month follow-up, the adjusted mean change (±standard error) in the OHS was 15.9±1.0 points in the THA group and 4.5±1.0 points in the PRT group (group difference 11.4 points [95% CI 8.9 to 14.0; P<0.001]).

Conclusion

Patient, clinician, and decision maker stakeholders had treatment expectations and beliefs that could lead to selection bias during enrolment procedures, treatment crossovers, and reduced generalisability of the randomised trial. To improve methodological rigorousness of the trial protocol, a parallel observational cohort was included, an enrolment procedure using generic guidance delivered by an independent clinician to facilitate communication of clinical equipoise was developed, and change in self-reported hip pain and function was selected as the primary outcome. A high quality randomised controlled trial comparing THA with PRT was designed, described, initiated, and completed with enrolment of 109 participants. At baseline, participants enrolled in the randomised trial had less self-reported hip pain and impairments in function, higher body mass index and fewer had previously received THA, TKA or supervised exercise than those enrolled in the parallel prospective observational cohort. Among individuals aged 50 years or above with severe hip OA considered eligible for surgery, THA yielded clinically significant superior improvements in hip pain and function compared with PRT at 6 months follow-up.

Dansk Resume

Introduktion

Hofteartrose er en væsentlig årsag til smerter og funktionsnedsættelse på verdensplan med dertilhørende store økonomiske omkostninger for samfundet. Hofteartrose rammer omkring 1 ud af 10, og det er den hyppigste årsag for total hoftealloplastik (THA). Hos personer med svær med hofteartrose anses THA, som en effektiv behandling til at reducere smerter, forbedre fysisk funktion samt øge livskvaliteten, men indgrebet er forbundet med lille risiko for alvorlige komplikationer. Omvendt er progressiv styrketræning (PRT) sikkert, og ser ud til at give moderate forbedringer i smerte, funktion og livskvalitet selv hos personer med svær hofteartrose. Indtil nu er THA aldrig blevet direkte sammenlignet med PRT. Denne sammenligning er yderst nødvendig, da ikke-kirurgisk behandling betragtes, som et alternativ til operation for mange muskuloskeletale lidelser.

Formål

Det overordnede formål var, at undersøge effektiviteten af kirurgisk og ikke-kirurgisk behandling hos personer svær med hofteartrose, der var vurderet egnet til THA. De specifikke studiers formål var:

Studie I. At udforske patient, kliniker og beslutningstager interessenters opfattelse af et randomiseret forsøg der evaluerer effektiviteten af THA sammenlignet med PRT med henblik på at informere udviklingen af forsøgsprotokollen.

Studie II. At udvikle og beskrive en forsøgsprotokol til et randomiseret forsøg, der sammenligner THA med et PRT program hos personer med svær hofteartrose.

Studie III. At evaluere om personer med svær hofteartrose, der blev inkluderet i et randomiseret forsøg, der sammenligner THA med PRT, adskilte sig i selvrapporterede karakteristika og effektmål scores fra dem

der kun accepterede inklusion i en parallel prospektiv observationel kohorte ved baseline.

Studie IV. At undersøge om THA forbedrede selvrapporterede hoftesmerter og funktion mere end PRT hos personer med svær hofteartrose fra baseline til 6 måneders opfølgning.

Materialer og Metoder

Studie I. Deltagere blev inkluderet i tre interessentgrupper: patienter med svær hofteartrose, der var vurderet egnet til THA, klinikere (ortopædkirurger og fysioterapeuter) og beslutningstagere (politikere og repræsentanter fra ikke-statslige interesseorganisationer). Fokusgruppeinterviews blev udført ved benyttelse af semistrukturerede interviewguides i henhold til gruppestatus. Interviews blev optaget, transskriberet ordret og analyseret tematisk ved brug af en induktiv tilgang.

Studie II. Der blev designet og beskrevet en protokol for et højkvalitets multicenter, parallelgruppe, randomiseret kontrolleret forsøg der sammenligner THA med PRT hos personer med hofteartrose, herunder overvejelser om studiedesign, inklusions- og eksklusionskriterier, rekrutteringsprocedurer, randomisering og metode til at skjule allokering, blinding, parallel prospektiv observationel kohorte, effektmål, interventioner, dataindsamling, stikprøvestørrelse og styrkeberegning og statistiske metoder.

Studie III. Der blev anvendt baselinedata fra det randomiserede forsøg (PROHIP) og den parallelle observationelle kohorte (Non-PROHIP). Deltagere-karakteristika og Oxford Hip Score, (OHS, score 0 [værst] til 48 [bedst], minimal klinisk relevant forskel [MID]=5 point), Hip disability and Osteoarthritis Outcome Score (HOOS) subskalaer (score 0 [værst] til 100 [bedst], MID=10 point) og University of Los Angeles aktivitetsscore (score [inakiv] til 10 [regelmæssig fysisk aktiv med høj belastning], MID=2 point) blev indsamlet ved benyttelse af elektroniske online spørgerskemaer. Data blev analyseret ved brug af deskriptiv statistik, standardiseret forskelle, ikk-parametriske tests og univariat logistisk regression.

Studie IV. Deltagere blev tilfældigt tildelt til at modtage enten en THA efterfulgt af standardbehandling eller et 12 ugers superviseret PRT program målrettet underekstremitetsmusklerne udført to gange om ugen efterfulgt af 12 ugers valgfri ikke-superviseret træning. Det primære effektmål var forskellen mellem grupperne i ændring i OHS (score 0 [værst] til 48 [bedst], minimal klinisk relevant forskel [MID]=5 point) fra baseline til 6 måneders opfølgning, analyseret ved brug af en mixed-effekt lineær regressionsmodel med gentagne målinger og justering for kovariater.

Resultater

Studie I. Der blev gennemført fire fokusgruppeinterviews med i alt 14 patienter, en fokusgruppe med 4 klinikere (2 ortopædkirurger og 2 fysioterapeuter) og en fokusgruppe med 4 beslutningstagere (3 politikere og 1 repræsentant fra en ikke-statslig interesseorganisation). To hovedtemaer blev udviklet. 'Behandlingsforventninger og overbevisninger påvirker valg af behandling' omfattede tre undertemaer: Behandling uden operation medfører formentlig ingen bedring; Klinikerens autoritet har indflydelse på behandlingsnarrativet; 'Operation versus træning' debatten. 'Faktorer der påvirker det randomiserede forsøgs integritet og gennemførlighed' fremhævede tre undertemaer: Hvem er egnet til operation?; Facilitatorer og barrierer for operation og træning i en randomiseret forsøgskontekst; Forbedringer i hoftesmerter og hoftefunktion er de vigtigste effektmål.

Studie II. THA interventionen bestod af et standardiseret fast-track multimodalt kirurgisk program, der inkluderede patientinformation, optimeret smertebehandling, og tidlig mobilisering. Den kirurgiske procedure blev udført i overensstemmelse med den posteriore adgang, og den postoperative rehabilitering fulgte hospitalsspecifikke procedurer. PRT programmet omfattede 10 minutters opvarmning på en stationær cykel, efterfulgt af fire øvelser der blev udført unilateralt i træningsmaskiner eller kabeltræk med størst mulig bevægeudslag. I hver øvelse blev der udført tre sæt med 60 sekunders pause i mellem. Progression af træningsbelastning fulgte en lineær model for periodisering med en initial relativ træningsbelastning på 12 repetitions maksimum (RM) i uge 1-2, 10RM i uge

3-6 og 8RM i uge 7-12. Den absolutte træningsbelastning blev justeret fra sæt til sæt ved at udføre kontraktion til muskeludtrætning og mellem sessioner justeret ud fra hoftesmerter.

Studie III. I alt blev 402 deltagere inkluderet i analysen med 109 i PROHIP og 293 i Non-PROHIP. PROHIP gruppen havde en bedre gennemsnitlig (±standard deviation) OHS (25.1±5.9 vs. 22.6±6.9, gruppeforskel 2.5 points [95% CI 1.1 til 4.0]) end Non-PROHIP gruppen. PROHIP gruppen havde også bedre gennemsnitsscores i alle HOOS subskalaer (gruppeforskelle var 4.9 point [95% CI 1.4 til 8.3] i HOOS smerter; 5.6 point [95% CI 1.9 til 9.3] i HOOS symptomer; 7.4 point [95% CI 3.5 til 11.3] i HOOS funktion i dagligdagsaktiviteter; 8.1 point [95% CI 4.0 til 12.2] i HOOS funktion i sport og fritid; og 7.7 point [95% CI 4.4 til 11.0] i HOOS livskvalitet), mens der var ingen forskel mellem grupperne i UCLA aktivitetsscore (gruppeforskel 0.2 point [95% CI -0.2 til 0.6]). For de selvrapporterede karakteristika havde PROHIP gruppen et højere body mass index (gruppeforskel 1.4 kg/m2 [95% CI 0.5 til 2.3]), og en lavere andel havde tidligere modtaget THA (gruppeforskel -13.5% point [95% CI -20.9 til -6.0]), total knæalloplastik (TKA) (gruppeforskel -6.4% point [95% CI -10.4 til -2.3]) eller superviseret træning (gruppeforskel -10.8% point [95% CI -21.0 til -0.7]) sammenlignet med Non-PROHIP gruppen.

Studie IV. Blandt de 109 randomiserede deltagere (gennemsnitsalder 67.6 år; 54 [49.5%] kvinder), gennemførte 103 (94.5%) det randomiserede forsøg. Ved 6 måneders opfølgningen var den justerede gennemsnitsændring (±standardfejl) i OHS 15.9±1.0 point i THA gruppen og 4.5±1.0 i PRT gruppen (gruppeforskel 11.4 point [95% CI 8.9 til 14.0; P<0.001]).

Konklusion

Patient, kliniker og beslutningstager interessenterne havde behandlingsforventninger og –overbevisninger, der kunne lede til selektionsbias under rekrutteringsprocedurer og overkrydsning af behandling samt reduceret generaliserbarhed af det randomiserede forsøg. For at forbedre den metodiske stringens af forsøgsprotokollen blev der

inkluderet en parallel prospektiv observationel kohorte, der blev udviklet en rekrutteringsprocedure med anvendelse af generisk vejledning leveret af en uafhængig kliniker med henblik på at facilitere en balanceret klinisk kommunikation og ændring i selvrapporterede hoftesmerter og funktion blev valgt som det primære effektmål. Et randomiseret kontrolleret forsøg af høj kvalitet, der sammenlignede THA med PRT, blev designet, beskrevet, påbegyndt og afsluttet med inklusion af 109 deltagere. Ved baseline havde deltagerne, der var inkluderet i det randomiserede forsøg, færre selvrapporterede hoftesmerter og funktionsnedsættelser, højere body mass index og færre havde tidligere modtaget THA, TKA eller superviseret træning end dem, der var inkluderet i den parallelle prospektive observationelle kohorte. Blandt personer i alderen 50 år eller derover med svær hofteartrose der var vurderet egnet til operation, gav THA klinisk signifikante større forbedringer i hoftesmerter og funktion sammenlignet med PRT ved 6 måneders opfølgning.

Introduction

Osteoarthritis

Osteoarthritis (OA) is a whole joint disorder characterised by structural alterations in the articular cartilage, subchondral bone, ligaments, joint capsule, synovial membrane, and periarticular muscles.[1-4] This musculoskeletal disorder is a leading contributor to pain, disability, and reduced quality of life among individuals aged 50 years and above.[5 6]

Epidemiology

Worldwide, an estimated 528 million people are currently affected by OA.[5 7] Between 1990 and 2017, the prevalence of OA has raised by 9.3%, and this development is anticipated to continue in the future due to increased life expectancy and ageing of the global population.[5]

The economic consequences related with OA are substantial, both in terms of healthcare costs (e.g., primary care visits, visits to specialists, diagnostic tests, hospitalization, analgesics, and surgery) and non-healthcare-related costs (e.g., productivity losses, formal care, and informal care). The overall socio-economic costs of OA in high-income countries has been estimated to account for between 0.25% and 0.50% of the gross domestic product of these countries.[8]

The most frequently affected joint is the knee followed by the hand and hip.[7 9] For hip OA, the reported prevalence varies widely from 1% to 45% depending on age categories, setting (i.e. hospital-based or population-based), countries of origin, and definition used to classify hip OA (i.e., self-reported, radiographic or symptomatic).[10] In this context, the prevalence of symptomatic hip OA is considerably lower than for radiographic hip OA,[10 11] with estimates ranging between 1% and 10% in the population.[10 12 13] Over the last three decades, the total number of years lived with disability caused by hip OA has increased by 127%, reflecting an increasing major global-health burden.[14]

Risk factors

Several risk factors have been identified for the development of hip OA.[2 13 15 16] These may be divided into person-level risk factors including age, sex, obesity, genetics, occupation and sports activity, and joint-level risk factors comprising hip joint morphology, muscular function, and joint injury.[13 17]

Person-level risk factors

Age is considered the main and strongest risk factor for hip OA. [2 13 15] The incidence and prevalence of hip OA increases with age,[5 7] probably as a result of cumulative exposures to different risk factors and biological age-related changes in the joint structures.[16]

Female sex is commonly assumed as an important risk factor for OA and the role of oestrogens has been widely investigated, but the mechanism still remains unclear.[5 7 15 16] For hip OA, this association is less evident than for knee and hand OA, and results are generally inconsistent.[5 10 12 13 15-19]

Obesity is another risk factor that contributes to the development and progression of OA.[2 15-17 20] The evidence of an association between obesity and hip OA is to some extent contradictory,[2 13 15 17 20-25] but a dose response-relationship exists with each five-unit increment in body mass index increasing the risk of hip OA with 11%.[13 26] Two mechanisms or a combination of both are proposed to explain this link.[13 15 17] First, higher body weight increases the biomechanical load at the hip joint, which leads to larger joint stresses. Second, obesity increases joint sensitivity through the effects of inflammatory and metabolic factors. The metabolic hypothesis is supported by a link between obesity and hand OA, although the hand is not a weight-bearing joint.[13 17]

Genetics factors are substantial contributors for hip OA as these are estimated to account for approximately 60%.[13 17] Multiple genetic mutations have been identified and associated with an increased risk of hip OA,[13 15 27] and these are suggested to exist on a continuous spectrum related to joint morphology of the hip joint. In this regard, early-onset hip OA is caused by mutations in matrix molecules commonly linked to markedly abnormal joint morphology such as chondrodysplasias, while mutations of

less prominent joint abnormalities increase predisposition to injury and malalignment, resulting in middle-aged onset hip OA. Lastly, mutations in molecules regulating subtle aspects of joint development and joint morphology may lead to late-onset hip OA.[13 27]

Occupations that involves long-term exposure to high levels of physical demanding tasks or heavy manual labour, especially in the farming or construction industry is associated with hip OA.[2 13 25 28 29] This may be due to repetitive high-impact joint loading causing increased biomechanical stress to the hip joint.[13]

Long-term participation in elite level high-impact sports such as football, handball, hockey, and track and field increases the risk of developing hip OA.[2 13 17 30] This association could be confounded by higher rates of traumatic injuries in elite level athletes as a result of their sports participation,[13 17] but two mechanisms may explain this predisposition to an increased risk of hip OA. First, increased repetitive high-impact joint loading as described for obesity and heavy manual labour. Second, increased prevalence of cam morphology at the femoral head-neck junction, which may be due to exposure to high levels of physical activity in a crucial phase of the osseous development during adolescence.[13 15]

Joint-level risk factors

Hip joint morphology abnormalities such as hip dysplasia and femoroacetabular impingement are considered significant risk factors for hip OA.[2 13 15 18] In hip dysplasia, the acetabular coverage of the femoral head is decreased causing a distribution of shear forces anterosuperiorly in the hip joint that over time may lead to degeneration of the acetabular labrum and articular cartilage. In femoroacetabular impingement, two different morphological patterns exist, and these are cam and pincer.[13 31] The principal morphological abnormality is thickened aspherical femoral head-neck junction in cam, and acetabular over coverage of the femoral head in pincer. Despite these pathogenic differences between cam and pincer, both types cause abnormal contact within the hip joint, in which degeneration of the acetabular labrum and articular cartilage may develop over time.[13 15]

Muscular impairment of the deep stabilising muscles of the hip joint is assumed to play a part in pathological joint biomechanics, as these muscles probably act as protectors for the hip joint.[13 16] Muscle weakness of the hip and lower extremity is associated with hip OA, but whether this is a cause or an effect of hip OA remains unclear.[13 32-37]

Joint injury is associated with a considerably increased risk predisposing to hip OA.[13 20 25 29 38] In the hip, an acetabular labral tear is a prevalent joint injury either due to acute trauma or degenerative changes over time.[13] Joint injury may impose bone or cartilage damage, which is likely to make the hip more sensitive to joint loading or alter the biomechanical environment contributing to the development of hip OA.[13 15]

Pathogenesis

The pathogenesis of hip OA is complex and multifactorial involving a combination of mechanical, inflammatory, and metabolic factors, which eventually lead to structural degeneration of the synovial joint. The disorder is not a passive degenerative or wear-and-tear disorder as frequently described, but rather an active dynamic alteration caused by an imbalance between degradation and repair of joint tissues.[2 3 15 39]

In this pathogenic process, the hyaline cartilage composition changes leading to loss of cartilage integrity.[2 40] The compositional changes modify the cartilage material properties and increase its sensitivity to disruption induced by biomechanical loading.[2 3 40] At first, erosions are located solely at the surface, but later on profounder fissures in the cartilage develop, and the calcified cartilage zone expands.[2] In an effort at tissue repair, the hypertrophic chondrocytes display increased activity resulting in an elevated production of proinflammatory mediators and matrix degradation products, which both inhibit chondrocyte function and affect the nearby synovial membrane to stimulate proliferative and proinflammatory responses.[2 3 40] In this context, the proliferating synoviocytes located in the synovial membrane contributes with an additional production and release of proinflammatory mediators leading to tissue hypertrophy and increased vascularity.[2 3 40] Simultaneously, there is an increased bone turnover within the subchondral bone combined with

the manifestation of vascular invasion into the hyaline cartilage. This bone remodelling and repair process is also related with development of subchondral sclerotic bone marrow lesions.[2 3 40] The osteophyte formation found at the joint margins is a result of reactivation of endochondral ossification, which is highly influenced by inflammatory biological factors as well as exposure to high-levels of biomechanical overload and abnormal joint kinematics.[2 41]

Since a wide range of underlying mechanisms and pathways ultimately lead to similar joint degradation, hip OA may be regarded as a syndrome rather than a single disorder.[2] Each of the risk factors may initiate a different mechanistic pathway leading to hip OA. Consequently, the mediators that facilitate the development of hip OA among older individuals may differ from those that contribute to hip OA in individuals with obesity or in individuals with younger age having suffered from a joint injury.[2]

Clinical presentation

Pain in the affected joint is the primary and most disabling symptom of hip OA.[2 3 42] Pain is the main driver used to guide clinical decision-making and is best outlined within a biopsychosocial model. Other common symptoms include joint stiffness, reduced range of motion, crepitus, joint instability (buckling or giving away), swelling, muscle weakness, fatigue, and pain-related psychological distress.[2 42]

There are two major types of pain in individuals with hip OA. The first is commonly described as a dull and aching pain that becomes persistent over time, and the other is characterised as an intermittent, intense, often unpredictable, and emotionally exhausting pain.[39 42 43] In the early stages of hip OA, episodes with pain are described as predictable and are often triggered by activity, while the pain becomes more persistent and starts to impact activities of daily living in moderate stages. In severe stages of hip OA, the persistent pain is substituted by brief episodes of intense and unpredictable pain resulting in substantial avoidance of activities, which also includes social and recreational activities.[39 42 43] Individuals with hip OA further describe their pain as having a more abrupt or rapid progression from mild to severe complaints, a more intense feeling (e.g., ice-pick,

pickaxe, spike, paralysing), and an increasing tendency to compare their pain with other extremely painful conditions (e.g., childbirth, broken bones or surgery) than individuals with knee OA.[39 43]

The pain mechanisms in hip OA are complex as pain often arises from a combination of peripheral nociceptive pain mechanisms, comprising increased responsiveness of peripheral nociceptors from ongoing tissue injury or inflammation in the joint, and neuropathic and central pain mechanisms.[2 41 42] Neuropathic pain emerges as a result of structural alterations in joint innervation or nerve changes within the peripheral nervous system or spinal cord, while central pain mechanisms involve increased activity in the descending pain facilitation pathways and loss of descending inhibitory nociceptive pathways.[2 42] Beside these neurophysiological mechanisms, the pain experienced by individuals with hip OA is influenced through a multidimensional and dynamic interaction between physiological, psychological and social factors that may modulate pain perception.[42]

Clinical assessment and diagnostic criteria

The diagnosis of hip OA is confirmed and defined either on the basis of the clinical presentation alone or in combination with radiograph imaging.[2 3 13 15 44] The clinical presentation without usage of radiographic imaging is considered sufficient for verifying the diagnosis of hip OA in clinical practice.[2 45] The clinical diagnosis is based on the individuals medical history and symptoms (family history of OA, activity-related hip pain, morning joint-related stiffness of the hip, and functional limitations) and a physical examination (posterior hip pain with squatting, groin pain on hip abduction or adduction, reduced range of motion of the affected hip, and hip abductor weakness).[2 44] In this context, it is recommended to use established diagnostic criteria such as those from the American College of Rheumatology (ACR)[46] or National Institute for Health and Care Excellence (NICE)[45] (**Table 1**). Radiographic imaging is either used to confirm the diagnosis or monitor disease progression of hip OA, and pathologic features include narrowing of the joint space width, osteophyte formation and the development of subchondral sclerosis and cysts.[13 15]

Table 1. American College of Rheumatology (ACR)[46] and National Institute for Health and Care Excellence (NICE)[45] diagnostic criteria for verifying the clinical diagnosis of hip osteoarthritis.

ACR clinical criteria A	ACR clinical criteria B	NICE criteria
Hip pain	Hip pain with internal rotation	Activity-related hip pain
AND	AND	AND
Hip internal rotation <15°	Hip internal rotation ≥15°	No morning joint-related stiffness or morning joint-related stiffness of the hip ≤30 min
AND	AND	AND
ESR ≤45 mm/h or hip flexion ≤115° if ESR is unavailable	Morning joint-related stiffness of the hip ≤60 min	Age ≥45 years
	Age >50 years	

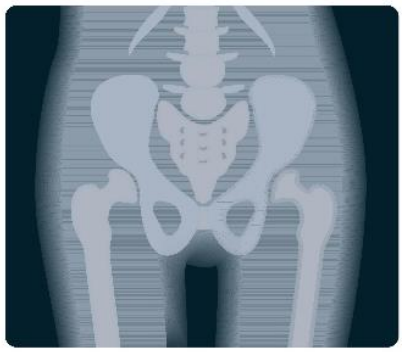
Erythrocyte sedimentation rate (ESR).

Radiographic verified hip OA is commonly assessed and classified for severity with the use of the scoring systems developed by Kellgren-Lawrence[47] and the Osteoarthritis Research Society International (OARSI)[48] (**Figure 1**). However, measurement of joint space width alone is considered the preferred method to evaluate structural severity, as it has similar validity and is more reproducible and sensitive to change compared with these two scoring systems.[15 49] It is important to note that there is a considerable discordance between hip pain and radiographic hip OA, as many individuals with radiographic findings of hip OA are asymptomatic, and correspondingly many of those with hip pain display no radiographic evidence of hip OA.[50 51]

Overall, the initial clinical assessment is advocated to comprise a comprehensive medical history and physical examination directed at identifying the influence of hip OA on physical function, quality of life, mood, social participation and relationships, occupation, recreational activities, sleep, and comorbidities. Furthermore, patient knowledge of the disorder, treatment options, previous experiences and expectations are important to explore.[2] Based on all of this information, an individual tailored treatment plan should be developed that accounts for the best available evidence and patient values in order to support a strong patient-clinician alliance with emphasis on engaging in shared-decision making.[2]

OARSI

Grade*	Radiologic findings
0-3+	Marginal osteophytes
	Superior acetabular
	Superior femoral
	Inferior femoral
No/yes	Inferior acetabular
0-3+	Joint space width narrowing
	Superior
	Medial
No/yes	Other
	Acetabular subchondral cyst
	Femoral subchondral sclerosis
	Flattening of the femoral head
	Thickening of the medial femoral calcar



Kellgren-Lawrence

Grade	Radiologic findings
0	No radiological findings of osteoarthritis
1	Doubtful narrowing of joint space width and possible osteophytic lipping
2	Definite osteophytes and possible narrowing of joint space width
3	Moderate multiple osteophytes, definite narrowing of joint space width, small pseudocystic areas with sclerotic walls and possible deformity of bone contour
4	Large osteophytes, marked narrowing of joint space width, severe sclerosis and definite deformity of bone contour

Figure 1. The Kellgren-Lawrence[47] and Osteoarthritis Research Society International (OARSI)[48] scoring systems for evaluating the severity of hip osteoarthritis. *Grade 0 (normal), 1 (mild change), 2 (moderate change), 3 (severe change).

Non-surgical and surgical treatment

Exercise and patient education

Multiple clinical guidelines have been developed, and all of them recommend supervised exercise and patient education as part of the core treatment in the non-surgical management of hip OA.[45 52-57] This recommendation is based on evidence from numerous randomised controlled trials and systematic reviews with meta-analyses that highlight various clinical benefits from supervised exercise and patient education including reduced pain, improved physical function, and increased quality of life.[58-60] Exercise and patient education has similar effects on hip pain and function as oral non-steroidal anti-inflammatory drugs and paracetamol.[61] In addition to these clinical benefits, exercise and patient education appear to be a cost-effective treatment approach,[62] which seem to decrease the willingness to undergo surgery by 30% and reduce the need for surgery by 44% after a treatment period of 12 weeks in individuals with hip OA.[63 64]

Supervised exercise interventions is also considered safe as there is a minimal risk of harm for individuals with hip OA.[65] In this regard, the most frequently reported adverse events are pain in another region, increased hip pain, muscle soreness, and numbness.[66] The effect of exercise on hip joint structures and articular cartilage is unknown,[65 67] but in individuals with knee OA exercise does not appear to increase cartilage thickness loss and molecular biomarkers related to cartilage turnover and inflammation associated with progression of OA nor to have a detrimental effect on the articular cartilage.[68-70]

Several different types of exercise such as aerobic, neuromuscular exercise, and progressive resistance training (PRT) are deemed useful in the management of hip OA,[45 52-57 65] as there is insufficient evidence to recommend and prescribe a specific type of exercise over another.[56 58 65 71]

Among individuals with hip OA, supervised exercise performed in accordance with The American College of Sports Medicine recommendations (ACSM) for exercise prescription in apparently healthy adults[72] (**Table 2**) may lead to larger improvements in pain and physical function than supervised exercise with uncertain prescription of exercise dose.[65 73] This finding highlights the potential importance of exercise dose and that exercise recommendations developed for healthy adults probably are relevant for individuals with hip OA.[73] In particular, supervised PRT with two to three weekly sessions performed using a minimum intensity of 60% of the 1 repetition maximum (RM) for 8-12 repetitions in sets of three per exercise may lead to clinically relevant improvements in hip pain, physical function, and quality-of-life in individuals with mild to severe hip OA.[74 75]

Table 2. The American College of Sports Medicine (ACMS) recommendations for exercise prescription in apparently healthy adults.[72]

Variable	Aerobic exercise	Resistance exercise	Neuromuscular exercise
Intensity/repetitions	Moderate intensity between 46-63% of maximal oxygen uptake for 30-60 min per day (150 min per week) or vigorous intensity between 64-90% of maximal oxygen uptake for 20-60 min (75 min per week)	Intensity between 40-≥80% of the 1 repetition maximum for 8-12 repetitions	An effective intensity of neuromuscular exercise has not been determined, but ≥20-30 min per day may be needed.
Bouts/Sets	Continuous or multiple bouts of ≥10 min	2-4 sets per exercise	Unknown
Frequency	3-5 days per week	2-3 days per week	2-3 days per week

Total hip arthroplasty

The first prosthetic total hip arthroplasty (THA) was developed by Wiles in 1938,[76] and this is considered as the precursor for the modern types of implants. In the 1960s, Charnley revolutionised the management of hip OA with the introduction of a THA with low friction torque using acrylic cement to fixate components to the bone and high-density polyethylene as a bearing material.[77] These modifications to the implant components showed a survival rate between 77% and 81% at 25 years of follow-up, which contributed to THA being acknowledged as the surgery of the century.[78] There is evidence from several randomised controlled trials, systematic reviews with meta-analyses, and international registries displaying that THA is as a highly effective treatment for reducing pain, and improving physical function and quality of life in individuals with severe hip OA.[79-83]

Hip OA is the leading cause for THA, accounting for 80% to 90% of the procedures in 2021.[84 85] Worldwide, more than 1 million THA surgeries are currently conducted each year and this number has increased by 37% in the period from 2008 to 2017.[86] In Denmark, around 10,250 primary THA surgeries are performed annually, and the yearly incidence rate has increased by 27% from 2008 to 2021.[84] The average age at primary THA surgery is 69 years, and the procedure is more commonly undertaken in females than in males with a stable ratio of 1.5:1 in the United Kingdom and Denmark.[84 85] Age at surgery has a substantial impact on the lifetime

risk of revision after primary THA, but most prosthetics nowadays have a durability of more than 18 years.[84-86]

Several indication criteria for THA based on limited evidence have been proposed,[87] but a recent effort has developed an algorithm and checklist of indication and contraindication criteria for shared-decision making on THA surgery.[88] A variety of surgical approaches are available, in which the NICE guideline recommends to consider using either the posterior or lateral approach for THA.[89] The posterior approach has shorter operation time and may lead to slightly greater improvements in physical function compared with the lateral approach.[83] Surgical management with THA is associated with a risk of serious adverse events (SAEs), and the most common leading to revision surgery include aseptic loosening, hip dislocation, periprosthetic joint infection, and periprosthetic fracture.[86] After THA surgery, the cumulative incidence of hip dislocations is 3.5% within 2 years,[90] and up to 23% report long-term residual pain.[91]

The NICE guideline on joint arthroplasty recommends that the inpatient postoperative rehabilitation is commenced on the day of surgery or no more than 24 hours after surgery to individuals undergoing a primary THA.[89] This postoperative rehabilitation should include advice on managing mobilisation and activities of daily living, and instruction in a home-based exercise programme.[89] For the outpatient postoperative rehabilitation, the Danish Health Authority and NICE guideline recommend to consider using supervised rehabilitation in individuals who have difficulties managing activities of daily living, ongoing functional impairment leading to specific rehabilitation needs, cognitive impairments or find that home-based rehabilitation is not meeting their rehabilitation goals.[54 89]

Rationale for this PhD thesis

Despite the high volume and increasing number of THA surgeries performed each year, no randomised controlled trial has compared THA directly with non-surgical treatment such as PRT in individuals with hip OA.[92 93] This comparison is highly wanted as non-surgical treatment is indicated as a viable alternative to surgery for many musculoskeletal

disorders due to no clinically relevant differences in pain, function, and quality of life between these treatments.[92 93] Among individuals with moderate to severe knee OA, a recent randomised controlled trial showed that total knee arthroplasty (TKA) was more effective in improving knee pain and functional impairments, but associated with a higher risk of SAEs than a non-surgical treatment programme, which included exercise and patient education after 1 and 2 years of follow-up.[94 95] On the other hand, 68% did not undergo TKA surgery in the non-surgical treatment group within this period.[94] Based on this, the findings from a direct comparison between THA and PRT in a randomised controlled setting is highly important in order to improve and support shared decision making in the discussion of treatment options between clinicians and individuals with hip OA in clinical practice.

Previous randomised controlled trials comparing surgical procedures with non-surgical treatments have had low enrolment rates between 7% and 26%.[95-99] This limitation potentially has an impact on the generalisability of these randomised controlled trials, making it unclear to which individuals the findings may apply for in clinical practice.[100 101] In addition, multiple patient and clinician barriers to participation in randomised controlled trials have been identified. Main patient barriers comprise additional demands of the trial, treatment preferences, worry caused by uncertainty, and concerns about information and consent, while key clinician barriers include time constraints, difficulty with the consent procedure, and lack of support staff and inadequate research training.[102]

Patient and public involvement include strategies for engaging key stakeholders in the design, conduct, and dissemination of research.[103] This has the potential to increase enrolment rates of participants and improve selection of outcome measures.[104 105] Although more than 90% of authors claim some kind of incorporation, only few randomised controlled trials involving surgical procedures within the orthopaedic area have reported use of patient and public involvement.[104 106]

Aim and Objectives

The overall aim was to investigate the effectiveness of surgical and non-surgical treatment in individuals with hip OA considered eligible for THA. The specific objectives of the studies in this PhD thesis were:

Study I

To explore patient, clinician, and decision maker stakeholders' perceptions on a randomised controlled trial evaluating the effectiveness of THA compared with PRT to inform the development of the trial protocol.

Study II

To develop and describe a trial protocol with explicit details for a randomised controlled trial that compared THA followed by standard care with a PRT programme in individuals with hip OA.

Study III

To evaluate whether participants with hip OA enrolled in a randomised controlled trial comparing THA with PRT differed in self-reported characteristics and outcome scores from those who only accepted enrolment in a parallel prospective observational cohort at baseline. The hypothesis was that participants enrolled in the randomised controlled trial would have less hip pain and impaired function than those who declined participation.

Study IV

To investigate whether THA improved self-reported hip pain and function more than PRT in individuals with hip OA from baseline to 6 months follow-up. The hypothesis was that THA would lead to superior improvements in hip pain and function compared with PRT.

Materials and Methods

The materials and methods of the individual studies (*Study I-IV*) in this PhD thesis are presented in the following section. There are some overlap between the studies, and any differences are outlined. An overview of the timeline and important milestones in this PhD thesis is depicted in **Figure 2**.

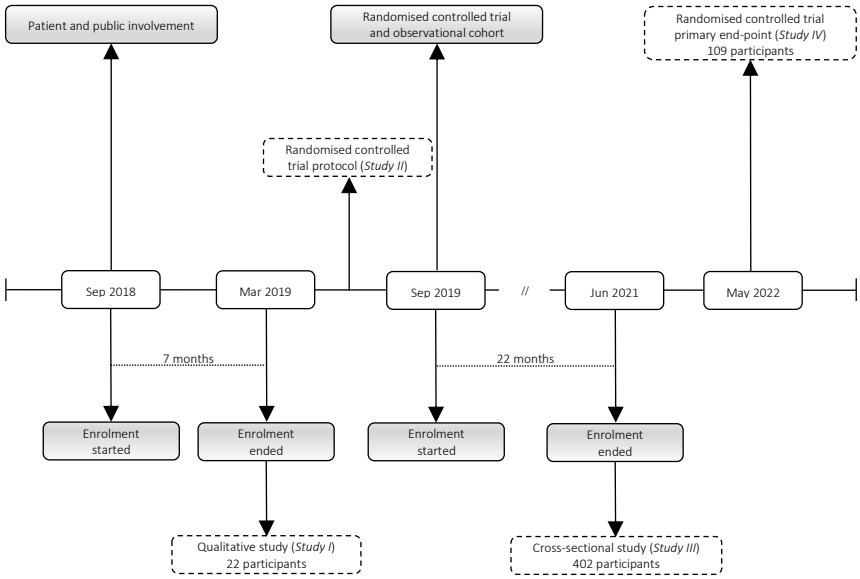


Figure 2. Overview of the timeline and important milestones in this PhD thesis.

Ethics, study registration, and reporting

Study I-IV

The *'PROgressive resistance training versus total HIP arthroplasty'* (PROHIP) trial (*Study II-IV*) was approved by The Regional Committees on Health Research Ethics for Southern Denmark (February 27, 2019 Project-ID: S-20180158), while no ethical approval was needed for the qualitative patient public involvement study (*Study I*), according to the Danish Act on Research Ethics. The Danish Act on Processing of Personal Data was followed, and the

studies was approved by The Danish Data Protection Agency (Journal No 18/23994 [*Study I*] and Journal No 19/20337 [*Study II-VI*]).

All the studies within this PhD thesis were conducted in accordance with the criteria and ethical principles of The Helsinki Declaration for medical research involving human participants.[107] All participants provided written informed consent before enrolment in the studies, and were informed that participation was voluntary, in which withdrawal of their consent were possible at any point in time without this influencing their current and future treatment rights.

The PROHIP trial was prospectively registered at ClinicalTrials.gov (August 28, 2019; NCT04070027) to ensure transparency and reduce selective outcome reporting. Statistical analysis plans were made publicly available at ClinicalTrials.gov before any statistical analyses commenced for *Study III* (August 3, 2022) and before the predefined stopping rule for participant enrolment was reached for *Study IV* (June 25, 2021).

The studies were reported in agreement with the Consolidated Criteria for Reporting Qualitative Research (COREQ)[108] checklist (*Study I*), Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[109] checklist (*Study II*), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[110] statement for cross-sectional studies (*Study III*), and Consolidated Standards of Reporting Trials (CONSORT)[111] statement (*Study IV*). In addition, the PRT intervention (*Study II, IV*) was described in accordance with the Consensus on Exercise Reporting Template (CERT),[112] and mechano-biological descriptors of resistance exercise stimuli as recommended by Toigo and Boutellier.[113]

Study design

Study I

This was an explorative qualitative case study using a constructivistic paradigm, as data was generated in collaboration between the investigators and participants during focus group interviews.[114] This approach was used to obtain a comprehensive understanding of a complex multidimensional

phenomenon by exploring the experiences, expectations, perceptions, and beliefs of the participants. Participants were enrolled into three different key stakeholder groups involved in the management of hip OA: patients (individuals with hip OA considered eligible for THA), clinicians (orthopaedic surgeons and physiotherapists), and decision makers (politicians or non-governmental organisation representatives) (**Figure 3**). These three key stakeholders groups were engaged at the level of consultation to attain input on numerous aspects of the subsequent randomised controlled trial, and implement the findings from this patient and public involvement strategy into the trial protocol.[115]

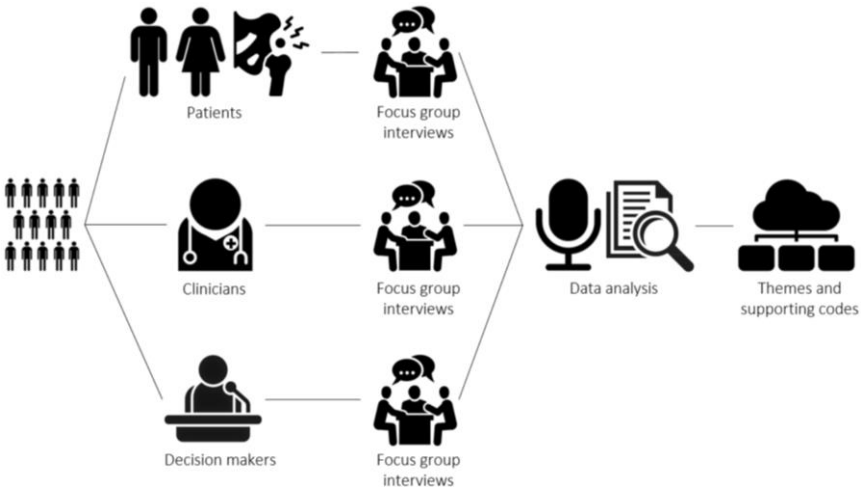


Figure 3. Schematic overview of the design of this explorative qualitative patient and public involvement study (*Study I*).

Study II

This was a protocol for a randomised controlled trial (PROHIP) comparing THA with PRT, which described the pre-specified considerations about study design, inclusion and exclusion criteria, enrolment procedures, randomisation and allocation concealment, blinding, parallel prospective observational cohort, interventions, outcomes, data collection procedures, sample size and power calculation, and statistical methods. See *Study IV* down below for the detailed study design description.

Study III

This was a cross-sectional study using baseline data from the randomised controlled trial (PROHIP) and a parallel prospective observational cohort (Non-PROHIP). In Non-PROHIP, all participants were scheduled for THA surgery and followed usual pre- and postoperative care procedures. The primary endpoint was the between-group difference in self-reported hip pain and function at baseline. Baseline measurements were obtained prior to randomisation for participants enrolled in the PROHIP trial, and before THA surgery for participants enrolled in the Non-PROHIP cohort (**Figure 4**).

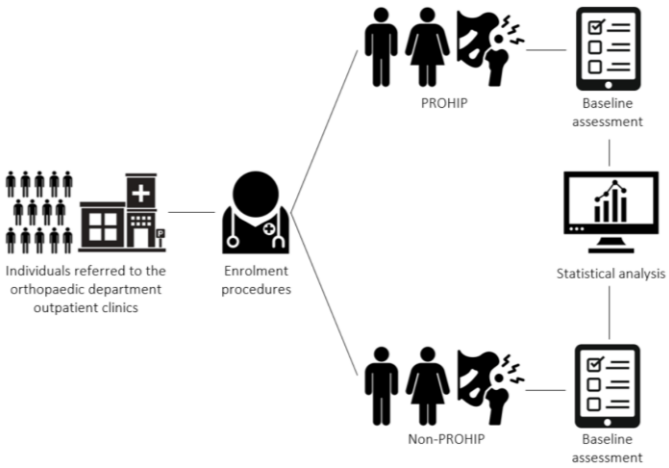


Figure 4. Schematic overview of the design of this cross-sectional study (*Study III*) using baseline data from the randomised controlled trial (PROHIP) and parallel prospective observational cohort (Non-PROHIP).

Study IV

This was an open-label, multicentre (four sites), stratified (by site), assessor-blinded, randomised controlled two parallel-group superiority trial with a 1:1 treatment allocation. Participants were randomly assigned to receive either THA followed by usual care or a supervised PRT programme. Outcomes assessments were conducted at baseline and at 3 and 6 months follow-up. The primary endpoint was the between-group difference in self-reported hip pain and function at 6 months follow-up after THA surgery or initiation of the PRT programme (**Figure 5**).

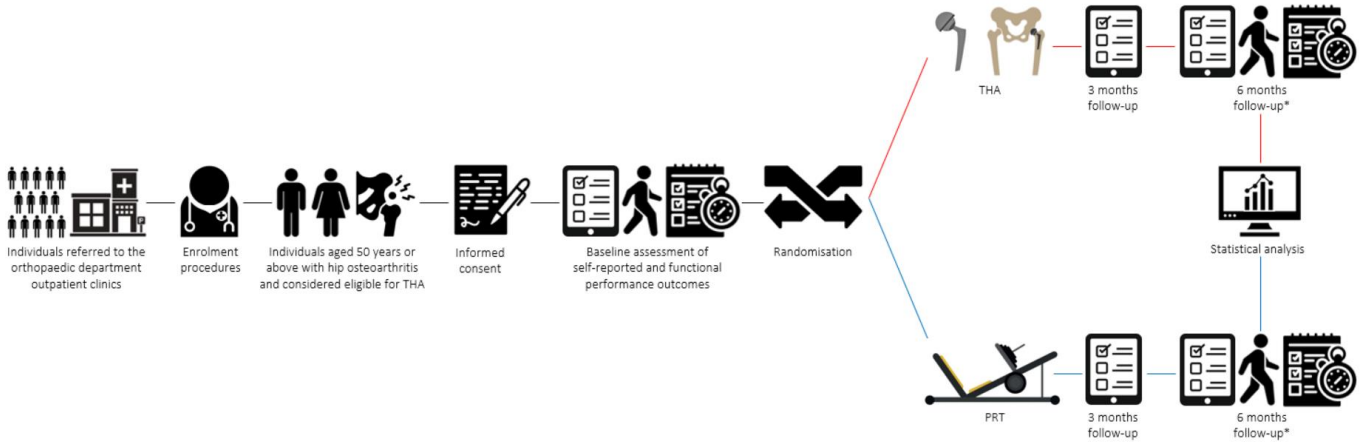


Figure 5. Schematic overview of the design of this randomised controlled trial (*Study IV*). * Denotes the primary endpoint. Total hip arthroplasty (THA). Progressive resistance training (PRT).

Setting

Study I

The focus groups interviews in the qualitative patient and public involvement study were conducted in undisturbed conference rooms at Vejle Hospital and Odense University Hospital in the Region of Southern Denmark from September 2018 to March 2019 (**Figure 6**). Besides the key stakeholder participants and interviewer, the principal investigator who was responsible of taking field notes was present during all focus group interviews.

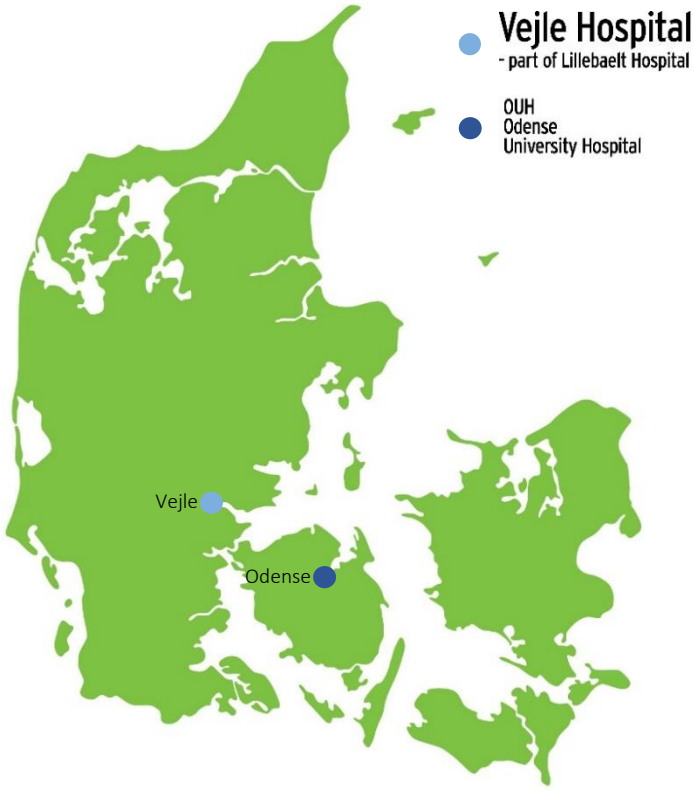


Figure 6. Overview of the orthopaedic department outpatient clinics involved in the conduct of the explorative qualitative patient and public involvement study (*Study I*).

Study II-IV

The cross-sectional study and randomised controlled trial were conducted at the orthopaedic department outpatient clinics at Vejle Hospital and Odense University Hospital in the Region of Southern Denmark, Aarhus University Hospital in the Central Denmark Region, and Næstved Hospital in Region Zealand from September 2, 2019 until the predefined stopping rule for participant enrolment was reached on June 30, 2021. In addition, the PRT intervention in the randomised controlled trial was conducted at municipal rehabilitation centres in Vejle, Kolding, Fredericia, Middelfart, Odense, Aarhus, Næstved, Slagelse, Korsør, Sorø, Roskilde, and Vordingborg (**Figure 7**).

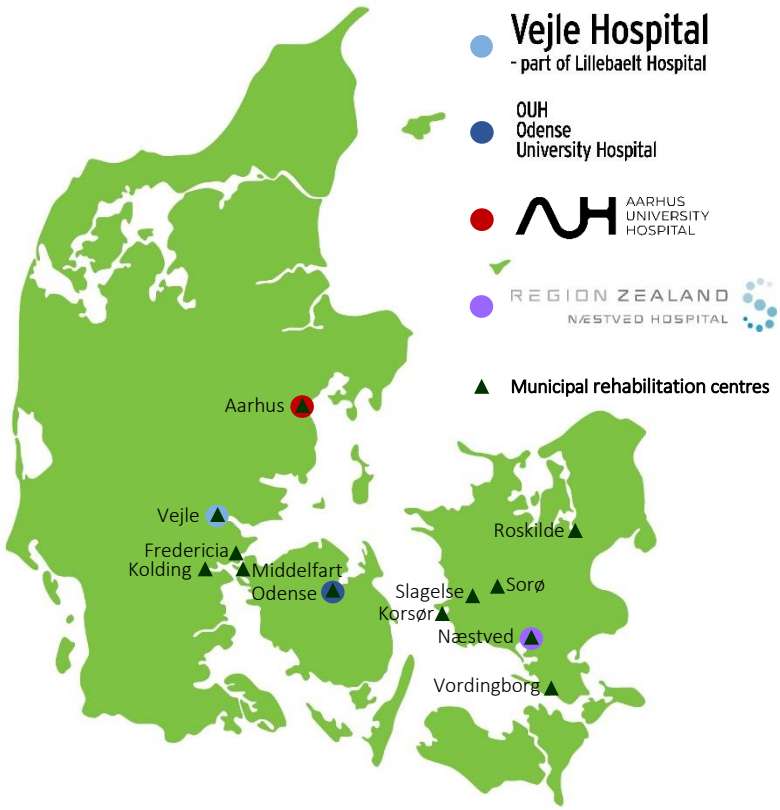


Figure 7. Overview of the orthopaedic department outpatient clinics and municipal rehabilitation centres involved in the conduct of the cross-sectional study and randomised controlled trial (*Study II-IV*).

Participants

Study I

A consecutive sample of individuals referred from primary care general practitioners to the outpatient clinics at Vejle Hospital and Odense University Hospital for evaluation for THA surgery were considered eligible as patient stakeholders if they fulfilled the detailed list of inclusion and exclusion criteria located in Study II-IV down below.

A convenience sample of orthopaedic surgeons and physiotherapists from Vejle Hospital and Odense University Hospital with more than two years of specialised clinical experience in the treatment of hip OA and not involved in the design of the randomised controlled trial were considered eligible as clinician stakeholders.

A purposive sample of politicians and non-governmental representatives with more than two years of experience from the spectrum of political parties and non-governmental organisations from the Region of Southern Denmark were considered eligible as decision maker stakeholders.

Study II-IV

Individuals referred from primary care general practitioners to the hospitals for evaluation for THA surgery were considered eligible for participation if they fulfilled the following inclusion and exclusion criteria.

Inclusion criteria were: (1) aged 50 years or above; (2) diagnosed with clinical and definite radiographic hip OA defined as narrowing of joint space width below 2 mm; and (3) considered eligible for THA (i.e., hip-related pain, symptom duration of more than 3 months, functionally impaired and/or decreased range-of-motion of the hip, and attempted treatment with analgesics). Exclusion criteria were: (1) severe walking deficits (i.e., dependency of two crutches or walker); (2) body mass index above 35 kg/m2, (3) lower extremity fractures within the previous 12 months; (4) planned lower extremity surgery in the following 6 months; (5) cancer diagnosis and receiving chemo-, immuno- or radiotherapy; (6) neurological diseases (e.g., previous stroke, multiple sclerosis, Parkinson's, Alzheimer's); (7) and other reasons (i.e., inability to speak or understand Danish, inability

to comply with the trial protocol (e.g., mental disorders, severe heart disease, and previous major lower extremity surgery within the previous 6 months).

Enrolment procedures

Study I

For the patient stakeholder group, orthopaedic surgeons assessed individuals for eligibility during the initial medical consultation at one of the two hospitals. Eligible individuals received face-to-face verbal and written information about the qualitative study delivered either by the orthopaedic surgeons or local study coordinators. For the clinician stakeholder group, an investigator assessed individuals for eligibility and delivered verbal and written information about the qualitative study after initial contact was established either face-to-face or through email correspondence. For the decision maker stakeholder group, an investigator assessed individuals for eligibility and delivered verbal and written information about the qualitative study after initial contact was established through email correspondence. Eligible individuals in all three key stakeholder groups who accepted enrolment in this study were scheduled for a focus group interview.

Study II-IV

Orthopaedic surgeons assessed individuals for eligibility during the initial medical consultation at one of the four hospitals. Individuals who were considered eligible for enrolment were briefly informed about the randomised controlled trial (i.e., trial objective and current knowledge gap) by the orthopaedic surgeons and given the option of receiving detailed verbal and written information provided by a local study coordinator in another undisturbed examination room. This detailed information covered the current evidence of treatment effects (i.e., THA and PRT), trial objective and treatment procedures, randomisation process, baseline and follow-up sessions, potential risk and harms, crossover and discontinuation procedures, clinical perspective and implications, and funding. All verbal information was delivered using standardised generic guidance, and the

orthopaedic surgeons and local study coordinators were instructed in this procedure to ensure that descriptions of both treatments were based on current evidence to reduce disclosures of personal opinions and facilitate communication of equipoise during enrolment procedures. Before deciding on participation, eligible individuals were recommended to consider and/or discuss participation with a family member or close contact for at least 24 hours. Eligible individuals who accepted enrolment in the randomised controlled trial were scheduled for baseline assessment and afterwards randomised to receive either a THA or PRT programme. Eligible individuals who declined to either receive detailed verbal and written information or participate in the randomised controlled trial were invited into a parallel prospective observational cohort. Those individuals who accepted enrolment were scheduled for THA and asked to complete self-reported baseline measures before the day of surgery.

Randomisation, allocation concealment, and blinding

Study II, IV

Participants were randomly assigned to receive either a THA or PRT programme in a 1:1 allocation ratio using a computer-generated randomisation schedule with variable block sizes from 2 to 6 and stratification for hospital. This allocation sequence was generated by an external data manager from Odense Patient data Explorative Network (OPEN) in Research Electronic Data Capture (REDCap),[116] and stored with no access from the investigators and local study coordinators. Treatment allocation was concealed until a local study coordinator pressed 'randomise' in REDCap, which was performed after baseline measurements were completed. Since this was an open-label randomised controlled trial, neither orthopaedic surgeons, nurses, and physiotherapists involved in the treatments nor participants were blinded to treatment allocation. Participants were not aware of the primary hypothesis being tested. Outcomes assessors conducted baseline and follow-up assessments blinded to treatment allocation. At the 6 months follow-up, participants were instructed in not revealing their allocated treatment, and to cover their

affected hip to conceal a potential scar after THA surgery. All investigators and the statistician were also blinded to treatment allocation.

Interventions

Study II, IV

Total hip arthroplasty

Participants received a multimodal standard fast-track THA (**Figure 8**) surgical program including preoperative patient information, optimised pain management, and early mobilization.[117] One to three weeks before THA surgery, participants were given in depth information about the surgical procedure, hospitalization, anaesthesia, and postoperative home-based exercise programme delivered by orthopaedic surgeons, nurses, and physiotherapists.

Figure 8. Total hip arthroplasty surgery.

On the day of surgery, participants were hospitalised and THA was performed by orthopaedic surgeons specialised in hip surgery using the posterior approach.[118] During this surgical procedure, participants were placed in the lateral decubitus position. First, an incision was performed over the posterior part of the greater trochanter through the fascia followed by blunt dissection of the gluteus maximus, and detachment of the external rotators. Then, a secondary incision was conducted over the posterior part of the hip joint capsule, with subsequent dislocation of the hip joint by internal rotation and flexion. Selection of component size was determined on preoperative templating using standardised pelvic and

anterior-posterior hip x-rays with final in vivo adjustments during surgery, if needed. Orthopaedic surgeons chose component types (i.e., cemented, uncemented or hybrid) and bearings, according to hospital-specific guidelines. Implants were inserted in line with manufacturer manuals. Finally, capsular repair and reinsertion of the external rotators were completed during closure of the wound.

Immediately after THA surgery, participants were allowed full weight bearing and after a few hours they were mobilised either to sitting or standing position. Participants received supervised inpatient rehabilitation, which comprised training and advice in managing transfer situations needed in activities of daily living (i.e., in-and-out of bed and sit-to-stand from a chair), gait with two crutches, stair walking, and instructions in a home-based exercise programme delivered by physiotherapists once or twice per day until the hospital-specific discharge criteria were achieved (**Table 3**).

Table 3. Discharge criteria and postoperative procedures at Vejle Hospital, Odense University Hospital, Aarhus University Hospital, and Næstved Hospital. This table is reused from the paper for *Study II*.

Criteria or procedures	Vejle Hospital	Odense University Hospital	Aarhus University Hospital	Næstved Hospital
In-and-out of bed	Independent	Independent	Independent	Independent
Sit-to-stand	Not described	Independent	Not described	Independent
Walking with assistive devices	Independent	Independent	Independent	Independent
Stair-walking	Independent	Independent	Independent	Independent
Basic activities of daily living	Independent	Sufficient	Independent	Independent
Understanding of the non-supervised home-based postoperative exercise programme	Sufficient	Independent	Independent	Independent
Referral to supervised postoperative rehabilitation	If necessary	If necessary	If necessary	Always
Postoperative control at the hospital	After 6 weeks at the physiotherapy department, if participants performed home-based postoperative rehabilitation	None	After 3 months at the orthopaedic department, if requested by participants	None

After discharge, participants followed hospital-specific procedures and performed a non-supervised home-based exercise programme or, if considered necessary, referred to supervised rehabilitation in line with national and international clinical guideline recommendations.[54 89] Satisfactory treatment adherence was defined as reception of THA (100%). The hospital-specific home-based exercise programmes are provided in **Appendix 1**.

Progressive resistance training

Participants received a 12 week supervised PRT programme with two weekly sessions at least 48 hours apart conducted at one of 12 municipal rehabilitation centres. Each session had a duration of approximately 60 minutes with one-to-one supervision delivered by physiotherapists. The standardised PRT programme included 10 minutes of warm-up performed on a stationary ergometer bicycle at an intensity equivalent to 14-15 (hard [heavy]) on the Borg Rating of Perceived Exertion Scale ranging from 6 (no exertion at all) to 20 (maximal exertion),[119 120] and four lower extremity exercises performed in the following order: leg press (**Figure 9**), hip extension (**Figure 10**), hip flexion (**Figure 11**), and hip abduction (**Figure 12**).

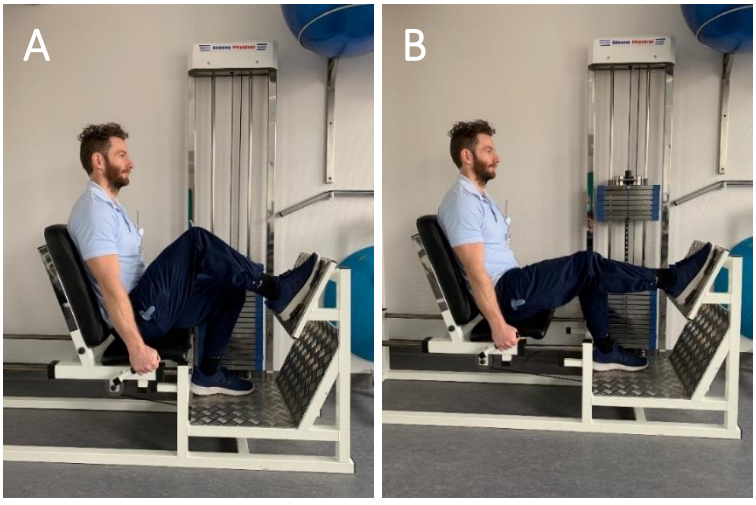


Figure 9. Leg press. Start position (A). End position (B). Images is reused from the paper for *Study II*.

Figure 10. Hip extension. Start position (A). End position (B). Images are reused from the paper for *Study II*.

Figure 11. Hip flexion. Start position (A). End position (B). Images are reused from the paper for *Study II*.

Figure 12. Hip abduction. Start position (A). End position (B). Images are reused from the paper for *Study II*.

All exercises were performed unilaterally for each leg to prevent unequal load distribution between legs in training machines or cable pulleys with as full-range-of-motion as possible. For each exercise, three sets were performed with 60 seconds of rest in between and progression of training load followed a classic linear model of periodization, with a relative load of 12RM in week 1-2, 10RM in week 3-6, and 8RM in week 7-12.[72 121] For each repetition of all exercises, the concentric phase was performed as fast as possible, full extension was subsequently maintained for one second, and the eccentric phase was completed in two to three seconds,[75 122] resulting in a total time under tension of five to six seconds per repetition (**Table 4**).

In the first PRT session, the main focus was to ensure that participants managed the proper technique and to determine the 12RM for each exercise. During all PRT sessions, the physiotherapists provided verbal encouragement and motivation, and the absolute training load was adjusted on set-by-set basis using muscular contraction to volitional concentric failure.

Table 4. Overview of the mechano-biological descriptors of the 12 week supervised progressive resistance training programme. This table is reused from the paper for *Study II*.

Variable	Week 1-2	Week 3-6	Week 7-12
Load magnitude	12 RM	10 RM	8 RM
Number of repetitions	12	10	8
Number of sets	3	3	3
Rest in-between sets	60 seconds	60 seconds	60 seconds
Sessions per week	2	2	2
Duration of training period	2 weeks	4 weeks	6 weeks
Contraction modes per repetition			
Concentric	As fast as possible	As fast as possible	As fast as possible
Isometric	1 second	1 second	1 second
Eccentric	2-3 seconds	2-3 seconds	2-3 seconds
Rest between repetitions	0 seconds	0 seconds	0 seconds
Time under tension per repetition	5-6 seconds	5-6 seconds	5-6 seconds
Volitional muscular fatigue	Yes	Yes	Yes
Range-of-motion	As large as possible	As large as possible	As large as possible
Rest between sessions	At least 48 hours	At least 48 hours	At least 48 hours
Anatomical definition of exercise	Yes	Yes	Yes

Repetition maximum (RM).

The absolute training load was increased if two or more repetitions than planned were completed or decreased if less than eight repetitions were conducted. Additionally, a hip pain management model was used to guide and adjust absolute training load between sessions.[75 123] In this model, self-reported hip pain at rest was assessed before, during, and after a training session on a Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable).[124] The interval from 0 to 2 was considered as 'safe', 3 to 5 as 'acceptable', and 6 to 10 as 'high risk' (**Figure 13**). The absolute weight load was decreased if the participants hip pain in the affected hip had not returned to pain as usual, defined as the level of pain before a training session, the day after a training session.[75 123]

Before the randomised controlled trial commenced, all the physiotherapists involved in delivering the PRT treatment attended a two-hour group-based training session and received a written protocol, which in detail described general information, progression principles, hip pain

management model, and each exercise with instructions. A project worker with previous experience in delivering supervised PRT for individuals with other musculoskeletal hip disorders and not otherwise involved in the trial audited training sessions at selected municipal rehabilitation centres twice with one month apart to ensure that the treatment was delivered in line with the protocol.

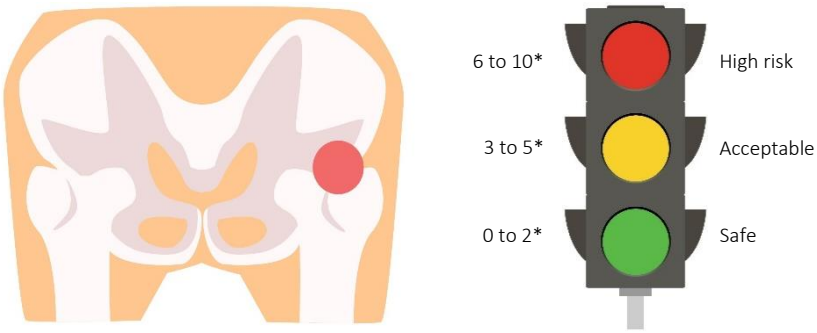


Figure 13. The hip pain management model.[75 123] * Self-reported hip pain at rest was rated before, during, and after a training session on a Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable).[124]

Following completion of the supervised 12-week period, participants were given the possibility of an additional 12 weeks of non-supervised PRT conducted at a public fitness centre or physiotherapy clinic of their own choice. In this context, participants received the written protocol and detailed instructions in the principles of the PRT programme. Satisfactory treatment adherence was defined as participation in 18 out of 24 supervised PRT sessions (75%). The PRT programme is provided in **Appendix 2**.

Treatment crossover and discontinuation

Study II, IV

Participants were informed that treatment crossover was allowed at any time during the trial period. In order to reduce the risk of treatment crossovers and discontinuation, physiotherapists involved in delivering the PRT treatment were instructed to verbally encourage participants to stay in

this group until at least the 12 week supervised period was finished, but preferably until after the additional 12 week non-supervised period and 6 months follow-up were completed. In this regard, physiotherapists provided information on transient exercise-induced pain flares and time frame for improvements in hip pain. This was highly important as it often requires at least 6 to 8 weeks for exercise-induced pain flares to diminish and before clinically relevant improvements are reported in individuals with hip OA.[75 125] Participants who experienced the PRT programme as ineffective or had an exacerbation of their hip pain and symptoms were contacted by a local study coordinator to discuss reassessment for THA with the orthopaedic surgeon performing the initial assessment during enrolment. As the participants were considered eligible for THA and that surgery is based on a shared-decision making process, no predefined criteria for crossover were established. Participants who either crossed over from PRT to THA or declined THA surgery after randomisation were asked to remain in the trial and complete follow-up assessments. Each reason for treatment crossover or discontinuation was registered in REDCap by the local study coordinators.

Outcomes

Patient and public involvement

Study I

The main outcome was to identify potential methodological improvement strategies for the design of the randomised controlled trial through focus group interviews with patient, clinician, and decision maker stakeholders and to implement the strategies that were considered feasible into the trial protocol.

Primary outcome

Study II-IV

For the cross-sectional study (*Study III*), the primary outcome was the between-group difference in self-reported hip pain and function at baseline measured using the Oxford Hip Score (OHS).[126] For the randomised controlled trial (*Study II, IV*), the primary outcome was the between-group

difference in change in self-reported hip pain and function from baseline to 6 months follow-up measured using the OHS. The OHS is a short 12-item questionnaire developed and designed to assess hip pain and function in one combined score in individuals with hip OA undergoing THA surgery.[126] Each item is rated on a Likert-scale from 0 (worst) to 4 (best), resulting in a total sum score ranging from 0 (worst) to 48 (best).[127] The OHS is possible to divide into hip pain (item 1, 8, 9, 10, 11, and 12) and hip function (item 2, 3, 4, 5, 6, and 7) subscales with each item rated in the usual way, resulting in raw sum scores between 0 and 24. These raw sum scores are then converted (i.e., 100/24 x actual raw score) to total subscale scores ranging from 0 (worst) to 100 (best).[128] The OHS has displayed excellent content validity, construct validity, internal consistency, test-retest reliability, interpretability, and responsiveness.[129-135] For the OHS total sum score, the minimal important difference (MID) between two groups is estimated to be 5 points.[129] A Danish cross-culturally adapted and validated version of the OHS was used in the studies.[135]

Key secondary outcomes

Study II-IV

Key secondary outcomes were the between-group differences at baseline (*Study III*) and in change from baseline to 6 months follow-up (*Study II, IV*) in self-reported pain, symptoms, function in activities of daily living, function in sports and recreation, and hip-related quality of life measured using the Hip disability and Osteoarthritis Outcome Score (HOOS) subscales.[136] The HOOS is a 40-item questionnaire consisting of five subscales developed for individuals with hip OA undergoing non-surgical treatment and THA.[136 137] Each item is scored on a Likert scale from 0 (best) to 4 (worst), and all subscale scores are normalised and converted, resulting in a subscale score ranging from 0 (worst) to 100 (best).[136] The HOOS has demonstrated adequate content validity, construct validity, internal consistency, test-retest reliability, interpretability, and responsiveness.[136-139] For all five HOOS subscales, the MID is considered to be 10 points.[140] A Danish cross-culturally adapted version of the HOOS 2.0 was used in the studies.[141]

Another key secondary outcome was the between-group differences at baseline (*Study III*) and in change from baseline to 6 months follow-up (*Study II, IV*) in self-reported physical activity level measured using the University of California Los Angeles (UCLA) activity score.[142] The UCLA activity score is a single-item questionnaire ranging from 1 (inactive) to 10 (regular physical activity with high intensity).[142] The UCLA activity score has shown questionable content validity, but satisfactory construct validity, test-retest reliability, and responsiveness in individuals with hip OA undergoing THA surgery.[143-145] For the UCLA activity score, the MID is presumed to be approximately 2 points, as it has not been formally established yet. A Danish cross-culturally adapted and validated version of the UCLA activity score was used in the studies.[143]

Study II, IV

Additional key secondary outcomes were the between-group differences in change in functional performance from baseline to 6 months follow-up assessed by the 40-meter Fast Paced Walk Test (40m-FPWT) and 30-second Chair Stand Test (30s-CST).[146] The 40m-FPWT measures gait speed in 4 x 10 meters (meters/seconds), and it is a valid and responsive test for assessing gait function (i.e., short distance maximum gait speed) with excellent intra- and interrater reliability.[146-148] The 30s-CST measures the total number of completed chair stands in 30 seconds (i.e., repetitions), and it is a valid and responsive test for assessing sit-to-stand function with moderate to excellent intra- and interrater reliability.[146-149] These two tests are recommended by OARSI as part of the minimum core set used in the assessment of performance-based function in individuals with hip OA.[146] The major clinically important improvement (MCII) is estimated to be 0.20 meters/second for the 40m-FPWT and 2.1 repetitions for the 30s-CST.[147]

Serious adverse events (SAEs) that occurred from baseline to 6 months follow-up, but which not necessarily had a causal relationship with the treatments were identified from reviewing the participants' hospital records and by self-report using a short custom made questionnaire. All SAEs were adjudicated for severity in accordance with the definitions from the International Conference on Harmonisation-Good

Clinical Practice (ICH-GCP) guidelines (i.e., any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation hospitalisation, results in persistent or significant disability or impairment, and results in congenital anomaly or birth defect),[150] and classified by an auditing committee consisting of an orthopaedic surgeon and nurse. Crossovers to THA surgery were not classified as SAEs.

Other outcomes

Study II-III

Other outcomes were the between-group differences at baseline (Study III) in self-reported hip pain intensity at rest and during activities measured using the Visual Analogue Scale (VAS).[124] The VAS is a valid, reliable, and responsive unidimensional measure of pain intensity ranging from 0 (no pain) to 100 (worst pain imaginable).[124] For the VAS, the minimal clinically important improvement is estimated to be 15.3 points in individuals with hip OA.[151]

Additional outcomes included the between-group differences at baseline in self-reported health-related quality of life measured using the EuroQol Group 5-dimension 5-levels (EQ-5D-5L) index score and overall health status measured using the EuroQol Group Visual Analogue Scale (EQ-VAS).[152] The EQ-5D-5L covers five dimensions including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has five levels of severity rated on Likert-scale from 1 (no problems) to 5 (extreme problems),[152] resulting in a five digit descriptive health state that is converted into the index score ranging from -0.757 (worst) to 1.000 (best) using a Danish value set.[153] The EQ-VAS is rated on vertical scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5L-5L and EQ-VAS are valid, reliable, and responsive measures of generic health-related quality of life and overall health status in individuals with a variety of chronic disorders including hip OA.[154-157] The MID is reported to be 0.41 points for the EQ-5D-5L index score and 9.34 points for the EQ-VAS.[155] An overview of the

primary, key secondary and other outcome measures used in the studies in this PhD thesis are presented in **Table 5**.

Table 5. Overview of the primary, key secondary, and other outcome measures used in *Study I-IV* in this PhD thesis.

Outcome measures	Scale or Unit	Domain
Primary outcome measure		
OHS	0 (worst) to 48 (best)	Self-reported hip pain and function
Key secondary outcome measures		
HOOS pain	0 (worst) to 100 (best)	Self-reported hip pain
HOOS symptoms	0 (worst) to 100 (best)	Self-reported other hip symptoms
HOOS ADL	0 (worst) to 100 (best)	Self-reported function in activities of daily living
HOOS sport/rec	0 (worst) to 100 (best)	Self-reported function in sports and recreation
HOOS QoL	0 (worst) to 100 (best)	Self-reported hip-related quality-of-life
UCLA activity score	1 (worst) to 10 (best)	Self-reported physical activity level
40m-FPWT	Meters/second	Performance-based gait function
30s-CST	Number of repetitions	Performance-based sit-to-stand function
SAEs	Type (yes/no)	Self-reported and hospital record registered harms
Other outcomes measures		
VAS	0 (best) to 100 (worst)	Self-reported mean hip pain intensity at rest and during activity
EQ-5D-5L	-0.757 (worst) to 1.000 (best)	Self-reported health-related quality-of-life
EQ-VAS	0 (worst) to 100 (best)	Self-reported overall health status

Oxford Hip Score (OHS); Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (sport/rec), and hip-related quality of life (QoL); University of California Los Angeles (UCLA) activity score; 40-meter Fast Paced Walk Test (40m-FPWT); 30-second Chair Stand Test (30s-CST); Serious Adverse Events (SAEs); Visual Analogue Scale (VAS); EuroQol Group 5-dimensions 5-levels (EQ-5D-5L); EuroQol Group Visual Analogue Scale (EQ-VAS).

Study II

As stated in the ClinicalTrial.gov registration and trial protocol, other outcomes that were collected also included self-reported Global Perceived Effect rated on a 15-Likert scale ranging from 'a very great deal worse' (worst) to 'a very great deal better' (best),[158] [159] Patient Acceptable Symptom State and Treatment Failure rated on a dichotomous scale (yes/no),[160] [161] analgesic consumption due to hip-related pain (yes/no: type

of analgesic; frequency), participation in optional non-supervised PRT (yes/no; content; duration; frequency); participation in postoperative supervised rehabilitation (yes/no; content; duration; frequency), other treatments related to the affected hip during the trial period (yes/no; type of treatment; duration; frequency), as well as isometric muscle strength (i.e., extension, flexion, and abduction) of the affected hip measured using a handheld dynamometer (Commander Echo Wireless Console and Muscle Tester, JTECH Medical, Salt Lake City, USA) procedure,[162] and accelerometer-based physical activity (AX3, Axivity, Ltd., Newcastle, United Kingdom).[163 164] These data are outside the scope of this PhD thesis, and are intended for subsequent secondary analyses presented elsewhere.

Data collection procedure

Study I

The qualitative data were collected through focus group interviews, which allowed the benefits of dynamic group interaction and in depth discussion of topics.[165] Each focus group interview included between two and five key stakeholder participants, had a duration from 90 to 120 minutes, and was performed face-to-face, according to group status. Based on the recommendations proposed by Krueger and Casey,[166] the principal investigator developed group-specific open-ended semi-structured interview guides (**Appendix 3**). The interviewer was a female physiotherapist, MSc with more than 10 years of specialised clinical orthopaedic experience, trained in qualitative methods, and had otherwise no involvement in the development or conduct of the randomised controlled trial. Prior to conducting the focus group interview, the interviewer had no previous interaction with any of the key stakeholder participants. Before each focus group interview was commenced, the interviewer disclosed her educational background and current profession. The interviewer also informed the key stakeholder participants about the study objective, current knowledge gap in the management of hip OA, as well as reasons for doing patient and public involvement in the development of a randomised controlled trial comparing THA with PRT. For the patient stakeholder group, the number of focus group interviews were

not predetermined, while one focus group interview was planned a priori for each of the groups with clinician and decision maker stakeholder participants due to time limitations. As multiple focus group interviews were conducted in the patient group, the semi-structured interview guide was continuously revised and adjusted after each focus group based on field notes taken by the principal investigator.

Each focus group interview was digitally audio-recorded, and subsequently transcribed and translated verbatim into English by an external linguist. Since it was assumed that the key stakeholder participants' reflective answers would develop during the focus group interviews, the transcripts and findings were not returned to them for comments and validation. In this regard, illustrative quotes from the focus group interviews are used to support statements and elucidate the generated themes and sub-themes. Characteristics of the key stakeholder participants were obtained using a self-reported custom-made questionnaire in paper format. In addition, the patient stakeholder group completed the OHS and HOOS. All data were pseudo-anonymised and stored in digital format on a password-protected hospital server (SharePoint Server 2019, Microsoft, Washington, USA) adhering to current data protection standards and requirements.

Study II-IV

Baseline characteristics and self-reported outcomes were collected using electronic online questionnaires in REDCap. At baseline and 6 months follow-up in the randomised controlled trial, participants completed the self-reported electronic questionnaires in undisturbed examinations rooms at the hospitals with the opportunity of asking clarifying questions, while an email with a link to the electronic questionnaires was sent to the participants who completed them at home at 3 months follow-up. At baseline in the parallel observational cohort, participants received the electronic questionnaires through an email and completed them at home. If participants had not completed the electronic questionnaires within three days, a reminder email was sent and subsequently contacted via telephone by a local study coordinator in case there were no response to the reminder

email. After completion of the electronic questionnaires in the randomised controlled trial at baseline and 6 months follow-up, outcome assessors assessed functional performance using a standardised test protocol. Before the data collection was commenced, all outcome assessors received a three hour training session in order to ensure equal performance and interpretation of each test in the protocol. An overview of the data collection in these studies is presented in **Table 6.**

Table 6. Overview of the data collection in the cross-sectional study and randomised controlled trial (*Study II-IV*). This table is reused from the paper for *Study II*.

Variables	Time-points				
	Enrolment	Baseline*	Allocation	3 months follow-up	6 months follow-up
Enrolment procedures					
Eligibility assessment	X				
Informed consent	X				
Randomisation			X		
Baseline measurements					
Participant characteristics		X			
Anthropometry		X			
Primary outcome measure					
OHS		X		X	X
Key secondary outcome measures					
HOOS pain		X		X	X
HOOS symptoms		X		X	X
HOOS ADL		X		X	X
HOOS sport/rec		X		X	X
HOOS QoL		X		X	X
UCLA activity score		X		X	X
40m-FPWT		X			X
30s-CST		X			X
SAEs				X	X
Other outcomes measures					
VAS		X		X	X
EQ-5D-5L		X		X	X

Table 6. Continued.

Variables	Time-points				
	Enrolment	Baseline*	Allocation	3 months follow-up	6 months follow-up
EQ-VAS		X		X	X
Global perceived effect				X	X
Patient acceptable symptom state				X	X
Treatment failure				X	X
Analgesics consumption		X		X	X
Optional non-supervised PRT					X
Postoperative supervised rehabilitation					X
Other treatments during trial period					X
Isometric hip muscle strength		X			X
Physical activity (accelerometer)		X			X
Treatment crossover					X

* In *Study III*, only data from self-reported outcome measures collected at baseline were used. Oxford Hip Score (OHS); Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (sport/rec), and hip-related quality of life (QoL); University of California Los Angeles (UCLA) activity score; 40-meter Fast Paced Walk Test (40m-FPWT); 30-second Chair Stand Test (30s-CST); Serious Adverse Events (SAEs); Visual Analogue Scale (VAS); EuroQol Group 5-dimensions 5-levels (EQ-5D-5L); EuroQol Group Visual Analogue Scale (EQ-VAS); Progressive Resistance Training (PRT).

Sample size and power calculation

Study I

Data saturation was used to guide the required sample size in the patient stakeholder group. This was considered accomplished if no new themes, sub-themes, perspectives or knowledge emerged within two consecutive focus group interviews. Since the number of focus groups were fixed to one in each of the clinician and decision maker stakeholder groups due to time limitations, the adequate sample size depended more on the concept of information power. This model involves an assessment of the contribution of novel data and input delivered by each participant rather than focusing on the number of participants (i.e., the more information a sample contains that is relevant for the specific study, the lower sample size is needed).[167]

Study II

The sample size and power calculation was based on the predicted between-group difference in the OHS mean change from baseline to 6

months follow-up. Based on data from international registries and previous studies, a mean baseline value between 14 and 23 points on the OHS was expected in individuals with hip OA considered eligible for THA.[79 80 127 129 168] A mean ±standard deviation (SD) improvement between 18 and 24±8 points in the OHS was anticipated in the THA group,[79 80 129] while a mean improvement between 10 and 15 points was considered plausible in the PRT group,[74 75] although this was deduced from other self-reported outcomes due to no available data on the OHS. Based on these assumptions, a total sample size of 120 with 60 participants in each group provided 92% power to detect a mean ±SD clinically significant difference between the two treatments of 5±8 points in the change score on the OHS using a two-sided alpha level of 0.05. To achieve at least 80% power, a total sample size of 84 with 42 participants per group was needed. A predefined stopping rule was established for this randomised controlled trial, in which a deadline was set 18 months after participant enrolment had commenced (i.e., February 28, 2021). This was later on prolonged 4 months (i.e., June 30, 2021) due to the coronavirus disease 2019 (COVID-19) pandemic, which resulted in a nationwide lockdown in Denmark decided by the Danish Government on March 11, 2020.

Study III

No formal sample and power calculation was performed for this cross-sectional study, since the enrolment ratio between PROHIP and non-PROHIP was unknown. Based on a previous randomised controlled trial that compared TKA with non-surgical treatment,[95] an enrolment rate of approximately 7% of all individuals assessed for eligibility was anticipated in PROHIP. This yielded that 1720 patients were required for eligibility assessment to include the estimated sample size of 120 participants in PROHIP. A two (14% ≈ 240 participants) to four (28% ≈ 480 participants) times higher enrolment rate was expected in non-PROHIP, resulting in an approximated total sample size between 360 and 600 participants for this cross-sectional study.

Study IV

The sample size and power calculation were identical with the trial protocol. See Study II above for the detailed description.

Qualitative data analysis

Study I

An external qualitative investigator not otherwise involved in the development or conduct of the randomised controlled trial performed a code book thematic analysis using an inductive approach without any predefined themes,[169] which followed the six-step framework proposed by Braun and Clark.[170] This procedure started with a familiarisation of the data by reading and re-reading the transcripts of each key stakeholder focus group interview. Then, initial codes were generated, which were based on line-by-line inductive coding performed on the transcripts. These initial codes were then used deductively to code subsequent focus group interviews, and as new codes were generated these were reapplied across all focus group interview transcripts in line with the constant comparison method.[171] As the data analysis progressed, the coding shifted from descriptive to explanatory, leading to a number of axial codes. These axial codes were organised and divided into preliminary main themes and sub-themes. This was followed by a critical review of the generated themes to ensure that these were coherent, distinct and supported by the data. The last steps in the analytic procedure involved final refinement of the main themes and sub-themes including development of the thematic network, and mutual discussion between investigators during the writing process about how these were described in the manuscript.[169 170] The data analysis was performed using Computer Assisted Qualitative Data Analysis Software (Atlas Ti, Version 8.0). After the thematic analysis was finalised, the developed main themes and sub-themes were presented to the PROHIP trial steering committee. Based on an evaluation of these findings, feasible methodological improvement considerations and strategies were identified and categorised in domains, and afterwards implemented into the trial protocol. Any disagreements in this process were resolved by discussion until consensus.

Statistical methods

Study I

The principal investigator performed the descriptive statistical analyses. All key stakeholder self-reported participant characteristics and outcome scores are presented with medians and range (min-max). Continuous variables were visually inspected with histograms and quantile-quantile plots to assess the assumption of normality, and the majority of variables did not follow a normal distribution. All descriptive statistical analyses and calculations were computed using STATA 16.0 (Statacorp, College Station, Texas, USA).

Study II

As this was the trial protocol, the statistical analysis was identical with the randomised controlled trial. See Study IV down below for the detailed statistical methods description.

Study III

The principal investigator conducted the statistical analysis in accordance with the publicly available statistical analysis plan (**Appendix 4**). All self-reported baseline characteristics and outcome scores are presented using descriptive statistics as mean with SD for continuous variables and number with proportion for categorical variables. Continuous variables were checked for normality using histograms and quantile-quantile plots.

The comparability of the PROHIP and non-PROHIP groups was assessed using balance diagnostics to evaluate potential differences in the baseline covariates between the groups.[172] In this approach, means for continuous variables and proportions for categorical variables were compared by estimating the standardised differences (STDdiff). A STDdiff of ≥0.20 was considered as an indication of a potential difference between the two groups, whereas ≥0.80 was interpreted as a definitive difference. In addition, Wilcoxon Rank-sum Test and Fisher's Exact Test were used to compute the empirical function statistics in order to assess the distribution of continuous variables and categorical variables, respectively. A P-value <0.05 was considered as a further indication of a potential difference

between the groups. Univariate logistic regressions were used to assess reasons and factors for accepting enrolment in the randomised controlled trial (i.e., Y=1 if an eligible individual accepted enrolment in PROHIP) by estimating the odds ratio (OR) for each self-reported baseline characteristic and outcome score variable.

Between-group differences of all variables are presented as means with 95% confidence intervals (CI). A 95% CI excluding a difference of 5 points or more in the OHS was interpreted as indicating absence of a clinically significant difference between the groups. All statistical analyses and estimations were performed using STATA 17.0 (Statacorp, College Station, Texas, USA).

Study IV

An external statistician who were not otherwise involved in the development or conduct of the randomised controlled trial performed the statistical analyses blinded to treatment allocation in agreement with the publicly available statistical analysis plan (**Appendix 5**). Based on blinded results from the intention-to-treat and single-step non-responder imputation sensitivity analysis (group A compared with group B), the PROHIP trial steering committee developed a signed consensus statement comprising two written blinded interpretations that was made publicly available (February 13, 2023) before breaking the randomisation code (**Appendix 6**), according to recommended procedures for blinded interpretation.[173] The SAEs, per-protocol, and as-treated analyses were conducted after breaking the randomisation code.

All baseline characteristics are presented using descriptive statistics as mean with SD or median with inter-quartile range (IQR) for continuous variables and number with proportion for categorical variables. Visual inspection of the standardised residuals from the statistical models were used to assess the assumption of normality and homogeneity of variances.

The primary and key secondary outcomes were analysed in line with intention-to-treat principle (i.e., all participants analysed with respect to their treatment allocation group as randomised regardless of

adherence, discontinuation or received treatment).[174] To account for multiplicity, the analyses of the key secondary outcomes were performed in a prioritised order (i.e., gatekeeping procedure) until one the analyses failed to display statistically significance or until all analyses were completed at a statistically significance level of P-value <0.05. The intention-to-treat analyses of the primary and key secondary outcomes included all participants randomly assigned to the two treatment groups, except for one ineligible participant who was randomised in error due to a personal mistake in the trial procedures. In the per-protocol analysis, participants who were randomised to THA receiving surgery, and participants who were randomised to PRT participating in 18 or more out of 24 sessions and not crossing over to surgery were included. In the as-treated analysis, participants receiving THA surgery were compared with participants not receiving THA surgery independent of randomisation group. In the last of the multiple sensitivity analysis, missing data were substituted using a single-step non-responder imputation approach with the baseline value carried forward.

Continuous primary and key secondary outcomes were analysed using a repeated measures mixed effects linear models with baseline score (one for each participant), treatment group (THA or PRT), time (baseline, and 3 and 6 months follow-up), hospital (Vejle, Odense, Aarhus, or Næstved), and interaction between treatment group and time as fixed effects. In addition, a participant-specific intercept and slope were included as random effects to account for within-individual measurement dependency. Categorical outcomes were analysed using logistic regression with identical fixed effect factors and covariates as used in the mixed linear model.

Missing data were managed indirectly and statistically modelled in the repeated measures mixed effects linear models. These models were considered valid if the outcome data were 'Missing at Random' (i.e., any systematic difference between the missing values and the observed values that could be explained by differences in the observed data).[175] For the intention-to-treat analyses, the following four point framework was used for making plausible assumptions about the missing data: (1) Attempt

to follow up all randomised participants, even if they withdrew from allocated treatment, (2) Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data, (3) Perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis, and (4) Account for all randomised patients, at least in the sensitivity analyses.[176]

A treatment responder analysis was performed for each participant on the individual OHS change score from baseline to 6 months follow-up. Two approaches were used to classify participants as treatment responders or non-responders. In the first approach, participants were classified as responders if the OHS improved by at least 8 points, corresponding to the minimal important change (MIC) at an individual level.[129] In the second approach, participants were classified as responders if the OHS pain or function subscales improved by 50% or more and by 20 points or more; or if two of the following three criteria were met: the OHS pain subscale improved by 20% or more and by 10 points or more; the OHS function subscale improved by 20% or more and by 10 points or more, or the OHS improved by 20% or more and by 10 points or more, according to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) set of responder criteria.[177]

Within-group changes from baseline to 6 months follow-up are presented as least squares means with standard error (SE) or medians with IQR, while between-group differences in change are reported as least squares means or medians with 95% CI and associated P-values. A two-sided P-value <0.05 was considered statistically significant. A 95% CI excluding a difference of 5 points or more in the OHS was interpreted as indicating absence of a clinically significant difference between the groups. Treatment response in each group is presented as numbers with proportions, while the between-group differences are reported as risk differences (RD) with 95% CI. Differences in the trajectories of OHS from baseline to 6 months follow-up are also presented. All statistical analyses and estimations were conducted in R version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Thematic network

Study I

In total, 4 focus group interviews with 14 patient stakeholders, 1 focus group interview with 4 clinician stakeholders (2 orthopaedic surgeons and 2 physiotherapists), as well as 1 focus group interview with 4 decision maker stakeholders (3 politicians and 1 non-governmental organisation representative) were performed (**Figure 14**). Self-reported participant characteristics of the patient, clinician, and decision maker stakeholder groups are presented in **Table 7**.

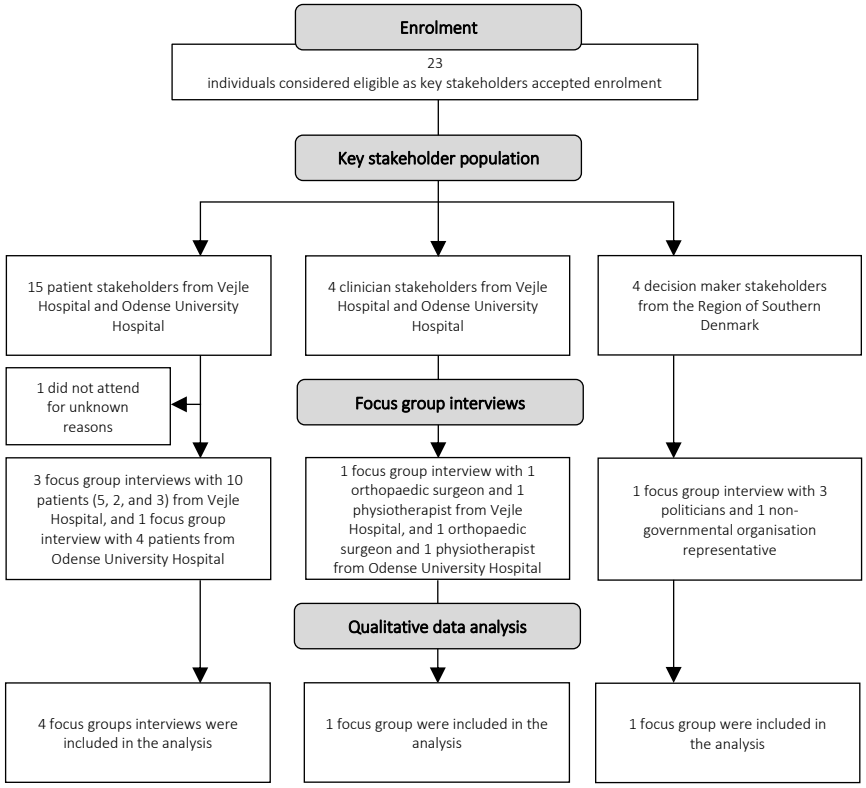


Figure 14. Flow of participants in this qualitative patient and public involvement study.

Table 7. Self-reported participant characteristics of the patient, clinician, and decision maker stakeholder groups.‡ This table is reused from the paper for *Study I*.

Characteristics	Patients (N=14)	Clinicians (N=4)	Decision Makers (N=4)
Female sex, n (%)	8 (57.1)	1 (25.0)	2 (50.0)
Age, years	68.5 (51.0-80.0)	48.0 (38.0-52.0)	56.5 (23.0-68.0)
Clinical and radiographic hip osteoarthritis, n (%)	14 (100.0)	0 (0.0)	0 (0.0)
Previous total hip arthroplasty, n (%)	3 (21.4)	0 (0.0)	0 (0.0)
OHS, 0 to 48	21.5 (10.0-38.0)	-	-
HOOS subscales, 0 to 100			
Pain	42.5 (20.0-77.5)	-	-
Symptoms	32.5 (15.0-80.0)	-	-
ADL	47.8 (20.6-86.8)	-	-
Sport/rec	25.0 (0.0-62.5)	-	-
QoL	31.3 (12.5-68.8)	-	-
Clinical profession, n (%)			
Orthopaedic surgeon	-	2 (50.0)	-
Physiotherapist	-	2 (50.0)	-
Clinical experience, years	-	16.0 (3.0-18.0)	-
Hospital affiliation, n (%)			
Vejle Hospital	-	2 (50.0)	-
Odense University Hospital	-	2 (50.0)	-
Political experience, years	-	-	5.0 (3.0-5.0)
Political or non-governmental affiliation, n (%)			
The Liberal Party of Denmark (V)	-	-	1 (25.0)
The Danish People's Party (O)	-	-	1 (25.0)
The Social Democratic Party (A)	-	-	1 (25.0)
The Danish Rheumatism Association	-	-	1 (25.0)

‡ Values are median (range) unless otherwise indicated; The Oxford Hip Score (OHS) ranges from 0 (worst) to 48 (best); The Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), hip-related quality of life (QoL), and function in sports and recreation (Sport/rec) range from 0 (worst) to 100 (best).

Two main themes were developed from the data analysis. Theme 1: 'Treatment expectations and beliefs impact management choices' covered three sub-themes: (a) Treatment without surgery is unlikely to lead to recovery; (b) Clinician authority impacts the management narrative; (c) The 'surgery versus exercise' debate. Theme 2: 'Factors influencing clinical trial integrity and feasibility' also highlighted three sub-themes: (a) Who is considered eligible for surgery?; (b) Facilitators and barriers for surgery and exercise in a clinical trial context ; (c) Improvements in hip pain and hip function are the most important outcomes (**Figure 15**).

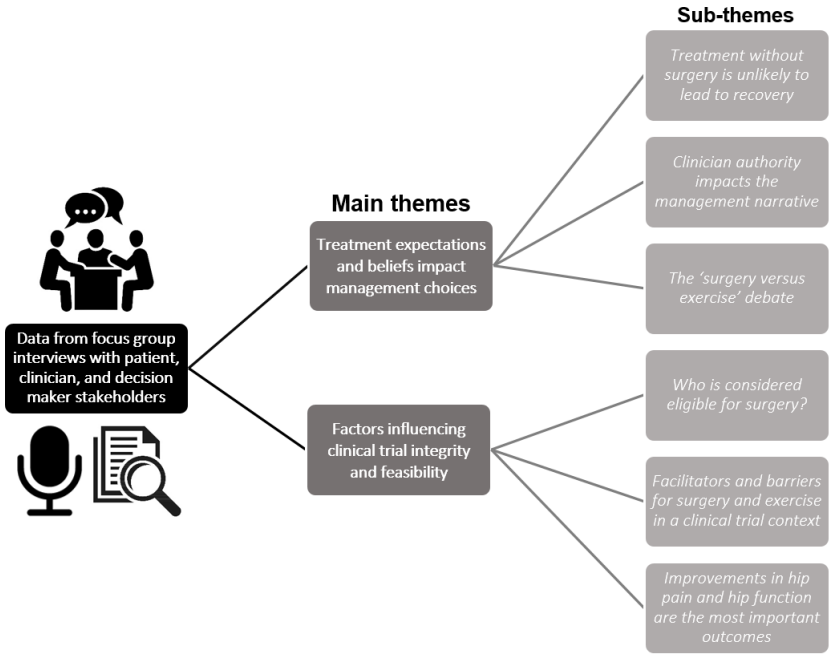


Figure 15. Thematic network including main themes and sub-themes. This figure is modified from the version used in the paper for *Study I*.

Theme 1: Treatment expectations and beliefs impact management choices

Treatment without surgery is unlikely to lead to recovery

For THA, patient stakeholders stated high expectations of complete abolishment of hip pain, quick return to preferred activities of daily living and recovery of functional performance approaching their pre-symptomatic level after surgery. For exercise, patient stakeholders had mostly uncertain and sceptical expectations, but they believed that exercise possibly could lead to improvements. Both patient and decision maker stakeholders perceived exercise as more appropriate in the management of mild and moderate stages of hip OA or considered it as an adjunct treatment to THA surgery in the pre- and postoperative phases to improve the outcome of THA. In general, patient stakeholders with severe hip pain and symptoms perceived themselves as greatly disabled and considered

treatment without THA surgery as unlikely in leading to their recovery. Illustrative quotes are provided in **Table 8**.

Clinician authority impacts the management narrative

Patient stakeholders expressed a great need of receiving face-to-face verbal information about the surgical and non-surgical treatment options by a competent and trustworthy clinician. In this context, orthopaedic surgeons were perceived as the clinicians with most authority. Orthopaedic surgeon stakeholders tended to describe THA surgery as a core treatment while they considered exercise as an adjunct treatment in the postoperative phase, and thus strengthened the perception of their status as the most authoritative clinicians due to virtue of their control over the THA surgery narrative. Patient stakeholders also emphasised that both orthopaedic surgeons and physiotherapists largely tended to use a management narrative suited to their favoured treatment, and occasionally this narrative was juxtaposed. Clinician stakeholders acknowledged the possible impact of their authority on individuals with hip OA perceptions of treatment effectiveness. This practice was highlighted with great concern for the randomised controlled trial, as the conduct of it relies on participants perceiving the effectiveness of THA and exercise as equal or almost equal treatments. Illustrative quotes are provided in **Table 8**.

The 'surgery versus exercise' debate

Clinician stakeholders were conscious about the ongoing debate and discourse, in which other surgical procedures and exercise were pitched against each other. This approach was perceived by both the orthopaedic surgeons and physiotherapists as completely out of context of reality, and agreed that fuelling a debate of selecting one treatment over another was not desirable, especially in the context of the randomised controlled trial. In this regard, an orthopaedic surgeon stakeholder highlighted it was important to develop a treatment narrative accentuating THA surgery and exercise as fundamentally different, but complementary rather than pitching the treatments against one another. Illustrative quotes are provided in **Table 8**.

Table 8. Theme 1 with sub-themes and illustrative quotes from key stakeholders.

Sub-themes	Theme 1: Treatment expectations and beliefs impact management choices
	Illustrative quotes
Treatment without surgery is unlikely to lead to recovery	'*I find it important to get rid of the pain, but also to get back to being physically active. Those two are equally important to me. I think. Because it used to be such a big part of my life'* (Patient 3, age 60-69 years).
	'*I have not been informed about the possibility of exercising the pain away*' (Patient 5, age 70-79 years).
	'*But if a hip is in a better state, then there is still a possibility to improve the person's condition without surgery. At the early stages of hip deterioration, exercise may seem like the best way forward*' (Decision maker 3, age 60-69).
	'*It is important to do exercise both before and after the surgery, to make your muscles as powerful as possible'* (Patient 1, age 60-69 years).
	'Having a defect hip is constraining both physically and mentally. Totally disabling.' (Patient 6, age 60-69 years).
	'I don't believe that it is possible to remove the symptoms just by means of exercising. I don't believe that is possible' (Patient 7, age 50-59 years)
Clinician authority impacts the management narrative	*'When I consulted the orthopaedic surgeon, the doctor. We were told absolutely everything about it [THA surgery], and he does it very well. There was no doubt in my mind*' (Patient 5, age 70-79 years).
	'*It is quite clearly "the surgery of the century". If the surgery is made on the right patient, it is both a safe and effective surgery. The degree of satisfaction is generally very high, both seen from the patients and the surgeons' perspectives'* (Clinician [Orthopaedic surgeon 2], age 40-49 years).
	'*The orthopaedic surgeon said: You can get a new hip, but I suggest you try to exercise for a period and then you can return to me when the pain gets too severe. The physiotherapists, they are very eager avoid surgery. At least the ones I have met, they have told me that I can exercise the pain away'* (Patient 2, age 50-59 years).
	'It is possible to talk about the different possibilities in a fairly objective way through a standardized text. And then it is important not to laugh… when the patient asks us, what would you choose?' (Clinician [Orthopaedic surgeon 2], age 40-49 years).
The 'surgery versus exercise' debate	'*This became quickly exercise against surgery, very much head-to-head and completely out of context of reality. We did not recognize, nor in the media the picture they created with the interpretation that you should rather exercise or carelessly get surgery*' (Clinician [Physiotherapist 2], age 30-39 years).
	'*But the question is whether surgery and exercise can be considered equal. Because surgery is dangerous, exercise is not very dangerous. Surgery is invasive, irreversible. Exercise is something you try out, and if it does not work, then you can have surgery*' (Clinician [Orthopaedic surgeon 2], age 40-49 years)

Theme 2: Factors influencing clinical trial integrity and feasibility

Who is considered eligible for surgery?

Patient stakeholders highlighted variations in symptoms of hip OA, but generally, they perceived radiographic findings such as narrowing of the joint space width, osteophyte formation, subchondral sclerosis and cysts were the primary indication of determining and selecting the surgical and non-surgical treatment approach. Since physiotherapist stakeholders had

observed substantial variation in levels of hip pain and functional impairments among individuals with hip OA scheduled for THA, they were sceptical and questioned the indication criteria used in current clinical practice for THA surgery. Orthopaedic surgeon stakeholders perceived that improvements in hip pain and functional performance obtained from exercise were associated with either an incorrect diagnosis or soft tissue pathology considered secondary to hip OA. Illustrative quotes are provided in **Table 9**.

Facilitators and barriers for surgery and exercise in clinical trial context

Based on key stakeholder responses, it appeared that younger individuals with hip OA were less likely to undergo THA surgery. This seemed to be driven by durability concerns of the THA implants and health beliefs. Patient stakeholders viewed THA and exercise as treatments to deliver pain management without usage of analgesics. In this context, THA surgery was clearly perceived as treatment to abolish severe hip pain, while less clarity was observed for exercise as residual hip pain both was highlighted as driver and barrier for continued treatment adherence. Exercise was perceived as a treatment associated with low risks of harms, whereas THA surgery was viewed as a last resort treatment with a slight risk of serious harms and complications. Patient stakeholders indicated that improvements experienced from exercise would most definitely encourage to continued treatment adherence, while unsatisfactory improvements in hip pain and activities of daily living at the end of an exercise programme were observed as drivers for THA surgery. Patient stakeholders indicated that they were considerably more likely to undergo THA surgery once presented with radiographic findings that visualised or displayed progression of their hip OA. Patient stakeholders also highlighted the importance of supervision in order to provide clinical expertise and motivation during training sessions, as well as establishing and maintaining exercise habits after the supervised period. Illustrative quotes are provided in **Table 9**.

Table 9. Theme 2 with sub-themes and illustrative quotes from key stakeholders.

Sub-themes	Theme 2: Factors influencing clinical trial integrity and feasibility	
	Illustrative quotes	
Who is considered eligible for surgery?	'*If a person is in pain and has a lot of cartilage left, then this person should be offered exercise and surgery should be postponed.* (Patient 1, age 60-69 years). '*At the information meetings, we see people who walk normally, and we then wonder why these people need new hips, because this person does not seem to be in pain, nor to be functionally impaired*' (Clinician [Physiotherapist 1], age 50-59 years). '*You need to be absolutely certain that the patient suffers from osteoarthritis. I believe that the patients who experience improvements by exercise, they suffer from a problem with the soft tissue. Something they have had in any circumstances or is secondary to the osteoarthritis*' (Clinician [Orthopaedic surgeon 1], age 50-59 years).	
Facilitators and barriers for surgery and exercise in a clinical trial context	**Facilitators for THA**	Illustrative quote(s)
	Severe hip pain	*'I am currently in a lot of pain, and I am looking forward to being released from that pain'* (Patient 1, age 60-69 years).
	Low quality of life	*'I cannot walk more than 100 meters, even with a cane'* (Patient 6, age 60-69 years).
	Ineffective first-line management	*'I have not been able to reduce my pain by means of exercise or physical activity, I need to have surgery to be able to live a tolerable life'* (Patient 6, age 60-69 years).
	Analgesics dependency	*'I ate so many pills, we agreed that something had to be done'* (Patient 2, age 50-59 years). *'They foresee that they will not be forced to take pills and at the same time, they will get well. Therefore, they choose surgery'* (Clinician [Orthopaedic surgeon 2], age 40-49 years).
	Diagnostic radiographic imaging	*When I got here the second time and saw the x-rays, I saw how much cartilage had disappeared since last time – in that short period of time - I said to myself that the actual bone may be next in line. I said to myself that there was no point in waiting any longer'* (Patient 2, age 50-59 years).
	Loss of livelihood	*'I may be rejected from the labour market because of my age, and I am not entitled to pension. So, I cannot afford not having surgery now'* (Patient 6, age 60-69 years).
	Barriers for THA	Illustrative quote(s)
	Patient age	*'…the uncertainty about whether the hip will last 10, 15, 20 years, and whether I will be able to get a new replacement at that time'* (Patient 2, age 50-59 years). *'I am also concerned about the durability of the total hip arthroplasty, because wearing out an artificial hip would result in a second surgery'* (Clinician [Physiotherapist 1], age 50-59 years).
	Risk of serious adverse events	*'A small risk of the surgery not being successful. That the pain ends up being much worse than before. I think that we all fear that… It would be so devastating if that should happen to us'* (Patient 2, age 50-59 years). *'Well, if the result is a foot drop, then I will not consider the surgery a success'* (Patient 7, age 50-59 years).

Table 9. Continued.

Sub-themes	Theme 2: Factors influencing clinical trial integrity and feasibility	
	Illustrative quotes	
Facilitators and barriers for surgery and exercise in a clinical trial context	**Facilitators for exercise**	Illustrative quote(s)
	Patient age	*'…people who feel too young to have hip surgery… because they see themselves as being physically active and capable of exercising the pain away'* (Clinician [Orthopaedic surgeon 2], age 40-49 years).
	Pain management without analgesics	*'Those four exercises are very valuable to me… I almost never take pills'* (Patient 2, age 50-59 years).
	Low risk of adverse events	*'It [exercise] will not harm them, and if they see improvements that is great.'* (Clinician [Orthopaedic surgeon 2], age 40-49 years).
	Perception of improvement	*'If I was able to feel a signification improvement after the 12-weeks exercise programme, then I would be motivated to continue'* (Patient 5, age 70-79 years).
	Maintaining exercise habits	*'Well, naturally I have spoken to other people about exercise, and I have asked them why they do not exercise, and they have a hard time getting started with it. Then I suggest that we go together, because the social aspect of it is very important, for some people at least'* (Patient 11, age 70-70 years).
	Supervision	*'It is also beneficial to have the presence of a professional person who can inform us about how the specific exercises help you, …where we are supposed to feel the pain if we do them correctly, which muscle is used and how to recognize this muscle'* (Patient 4, age 70-79 years).
	Context of exercise	*'I would appreciate to be in a place together with a group of people, where one person would instruct the others. And if you meet with a group of people several times, then you feel like being part of a community, and you can talk about the same things… That motives me'* (Patient 2, age 50-59 years).
	Tracking and gamification	*'It matters a lot, I think. Just like when you use a pedometer or a health app, I like that. I like to be able to see the result of my efforts… like Endomondo – get notified about having completed something'* (Patient 3, age 60-69 years).
	Barriers for exercise	Illustrative quote(s)
	Too severe or too mild hip pain	*'I have to say that when you are in pain, it is easy to exercise. But then when you don't feel pain, then you tend to forget to do your exercises one day, and then next day and so on. So, when everything is fine, then I have a hard time getting motivated to do exercises'* (Patient 1, age 60-69 years). *'Some people benefit a lot from exercise, but other people come back to me and explain that exercise only worsened the pain'* (Clinician [Orthopaedic surgeon 2], age 40-49 years).
	Low motivation	*'What is bad for me is that I always come up with a good excuse for not going… working out at home does not work for me, it is better if I go to a fitness centre with other people around'* (Patient 3, age 60-69 years).
	Continuity interruptions	*'…doing exercises in the fitness centre. But, I have also… Maybe I have taken some breaks, I could have put more efforts into it'* (Patient 3, age 60-69 years).
Improvements in hip pain and hip function are the most important outcomes	*My biggest problem is that I feel pain in all the different kinds of movements I do. No matter what kind of movement I do, I feel the pain'* (Patient 12, age 50-59 years).	

Improvements in hip pain and hip function are the most important outcomes
Both patient and clinician stakeholders highly indicated improvements in hip pain and hip function as the most important domains to assess the outcome of THA surgery and exercise. Both stakeholder groups also expressed performance-based gait function, quality-of-life, acceptable symptom state, muscle strength, treatment crossover, return-to-work, and leg-length discrepancy as other meaningful outcomes to measure in the randomised controlled trial. Illustrative quotes are provided in **Table 9**.

Methodological strategies implemented in the trial protocol

Study I

Based on the evaluation of the findings from the main themes and sub-themes, feasible methodological improvement considerations and strategies were developed and categorised across the following 4 generated domains: (a) patient 'buy in', (b) enrolment strategies, (c) patient information materials, and (d) important clinical outcomes.

Patient 'buy in'

Selection bias was identified as a possible risk to the external validity of the randomised controlled trial, as many individuals with hip OA who are considered eligible for enrolment probably may decline participation. In response, a parallel prospective observational cohort was conceptualised in order to assess and provide an indication of the generalisability of the trial. In addition, facilitators and barriers for THA surgery and exercise that could systematically influence retention rates and lead to treatment crossovers were addressed by developing a more focused discontinuation procedure (i.e., instruction of study personnel to encourage participant completion) and PRT protocol with effective one to one supervision during training sessions, and implementation of an optional non-supervised training period. These consideration also guided the development of the statistical analysis plan in regards to handling of missing data, and per-protocol and as-treated analyses.

Enrolment strategies

Preconceived beliefs and perceptions among clinician stakeholders were identified as possible risks to enrolment procedures in the randomised controlled trial, as these could lead to selection bias. To reduce disclosures of personal opinions and facilitate communication of equipoise during enrolment procedures, an instruction and training strategy in delivering standardised verbal information using standardised generic guidance with a neutral narrative was developed and implemented for orthopaedic surgeons and local study coordinators. This also guided selection of clinician roles during enrolment procedures, in which an independent clinician group was chosen as being responsible for delivering detailed verbal information due to clinical conflict of interests among orthopaedic surgeons and physiotherapists.

Patient information materials

Preconceived beliefs and perceptions among patient stakeholders guided the development of the written patient information materials. This covered the current evidence of treatment effects (i.e., THA and PRT), trial objective and treatment procedures, randomisation process, baseline and follow-up sessions, potential risk and harms, crossover and discontinuation procedures, clinical perspective and implications using a balanced and neutral narrative.

Important clinical outcomes

Patient and clinician stakeholder responses guided the selection of outcomes in the trial protocol. Change in hip pain and function was implemented as the primary outcome, while change in hip-related quality of life and functional performance (i.e., gait function) were applied as key secondary outcomes. Moreover, change in hip isometric muscle strength (i.e., extension, flexion, and abduction) and PASS were included as other outcomes. The four domains and their associated main themes and sub-themes, as well as the methodological considerations and strategies implemented into the trial protocol are presented in **Table 10**.

Table 10. Methodological considerations and strategies derived from the listed domains, main themes and sub-themes used to guide the development of the trial protocol. This table is reused from the paper for *Study I*.

Domain	Main themes	Sub-themes	Methodological considerations and strategies implemented into the trial protocol
Patient 'buy in'	Treatment expectations and beliefs impact management choices Factors influencing clinical trial integrity and feasibility	Treatment without surgery is unlikely to lead to recovery Clinician authority impacts the management narrative The 'surgery versus exercise' debate Who is considered eligible for surgery? Facilitators and barriers for surgery and exercise in a clinical trial context	Guided implementation of a parallel observational cohort in order to assess and provide an indication of the generalisability of the trial, as many individuals with hip osteoarthritis who are considered eligible for enrolment probably may decline participation. Guided development of discontinuation procedures (i.e., instruction of study personnel to encourage participant completion), statistical analysis plan (i.e., handling of missing data, per-protocol and as-treated analyses), and PRT protocol (i.e., effective one to one supervision during training sessions and inclusion of an optional non-supervised training period).
Enrolment strategies	Treatment expectations and beliefs impact management choices Factors influencing clinical trial integrity and feasibility	Clinician authority impacts the management narrative The 'surgery versus exercise' debate Who is considered eligible for surgery?	Guided development of an instruction and training strategy for orthopaedic surgeons and local study coordinators in delivering standardised information during enrolment procedures. Guided implementation of generic guidance with a neutral narrative during enrolment procedures to reduce disclosures of personal opinions and facilitate communication of clinical equipoise. Guided clinician roles during enrolment procedures and selection of an independent clinician group to provide detailed verbal information about the trial
Patient information materials	Treatment expectations and beliefs impact management choices Factors influencing clinical trial integrity and feasibility	Treatment without surgery is unlikely to lead to recovery Clinician authority impacts the management narrative The 'surgery versus exercise' debate Facilitators and barriers for surgery and exercise in a clinical trial context	Guided and informed the content for the written patient materials covering current evidence of treatment effects for surgery and exercise, trial objective and treatment procedures, randomisation process, baseline and follow-up sessions, potential risks and harms, crossover and discontinuation procedures, and clinical perspective and implications. Guided development of the balanced and neutral narrative used in the written patient materials to facilitate communication of clinical equipoise.
Important clinical outcomes	Treatment expectations and beliefs impact management choices Factors influencing clinical trial integrity and feasibility	Treatment without surgery is unlikely to lead to recovery Improvements in hip pain and hip function are the most important outcomes	Guided selection of change in hip pain and function as the primary outcome. Guided selection of change in hip-related quality of life and functional performance (i.e., gait function) as key secondary outcomes Guided selection of change in isometric hip muscle strength (i.e., extension, flexion, and abduction) and patient acceptable symptom state as other outcomes.

Self-reported characteristics and outcome scores at baseline

Study III

Participant enrolment

In total, 1474 individuals referred to the orthopaedic department outpatient clinics were assessed for eligibility (**Figure 16**). This yielded that 791 (53.7%) were deemed eligible for enrolment, and out of these 109 were enrolled in the PROHIP group (**Figure 17**). Among the remaining 681 individuals who declined participation in the randomised controlled trial, 293 were enrolled in the Non-PROHIP group (**Figure 18**). As a result, 402 participants completed baseline measurements and were included in the analysis (**Figure 19**). The enrolment rate of all individuals assessed for eligibility was 7.4% in PROHIP (**Figure 20**) and 19.9% in Non-PROHIP (**Figure 21**). This was equivalent to an enrolment ratio of 1:2.7. In addition, the enrolment rate of all individuals considered eligible was 13.8% in PROHIP and 43.0% in Non-PROHIP.

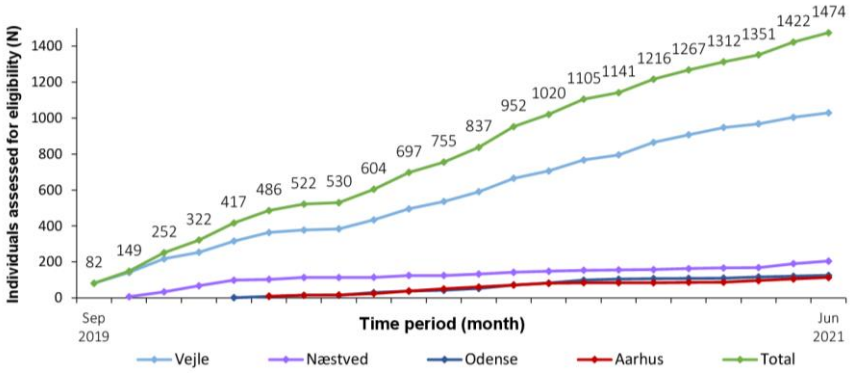


Figure 16. The total number of individuals assessed for eligibility. This figure is reused from the manuscript for *Study III*.

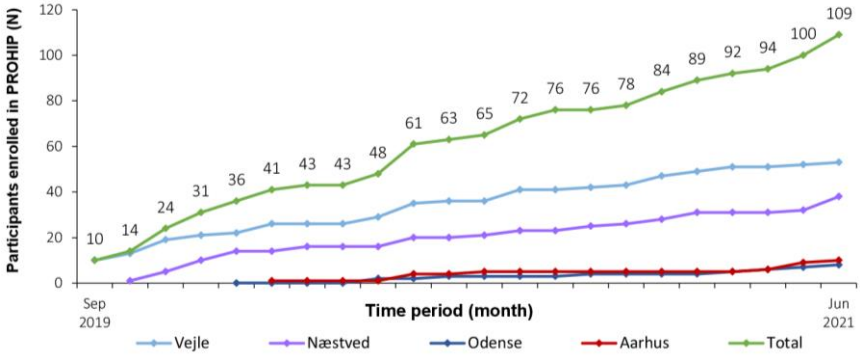


Figure 17. The total number of participants enrolled in the PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial. This figure is reused from the manuscript for *Study III*.

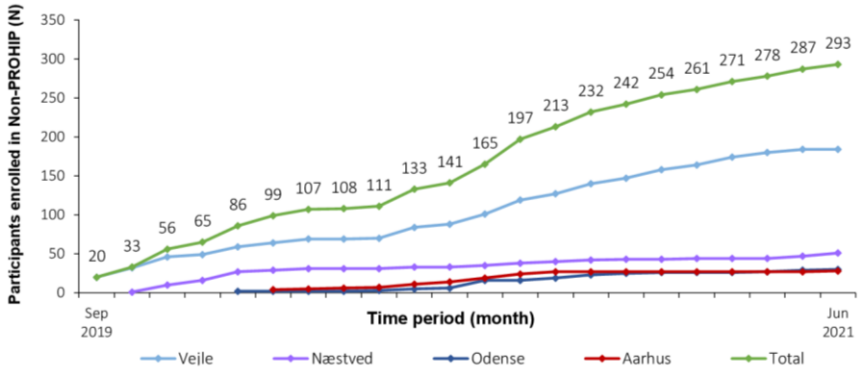


Figure 18. The total number of participants enrolled in the parallel prospective observational cohort (Non-PROHIP). This figure is reused from the manuscript for *Study III*.

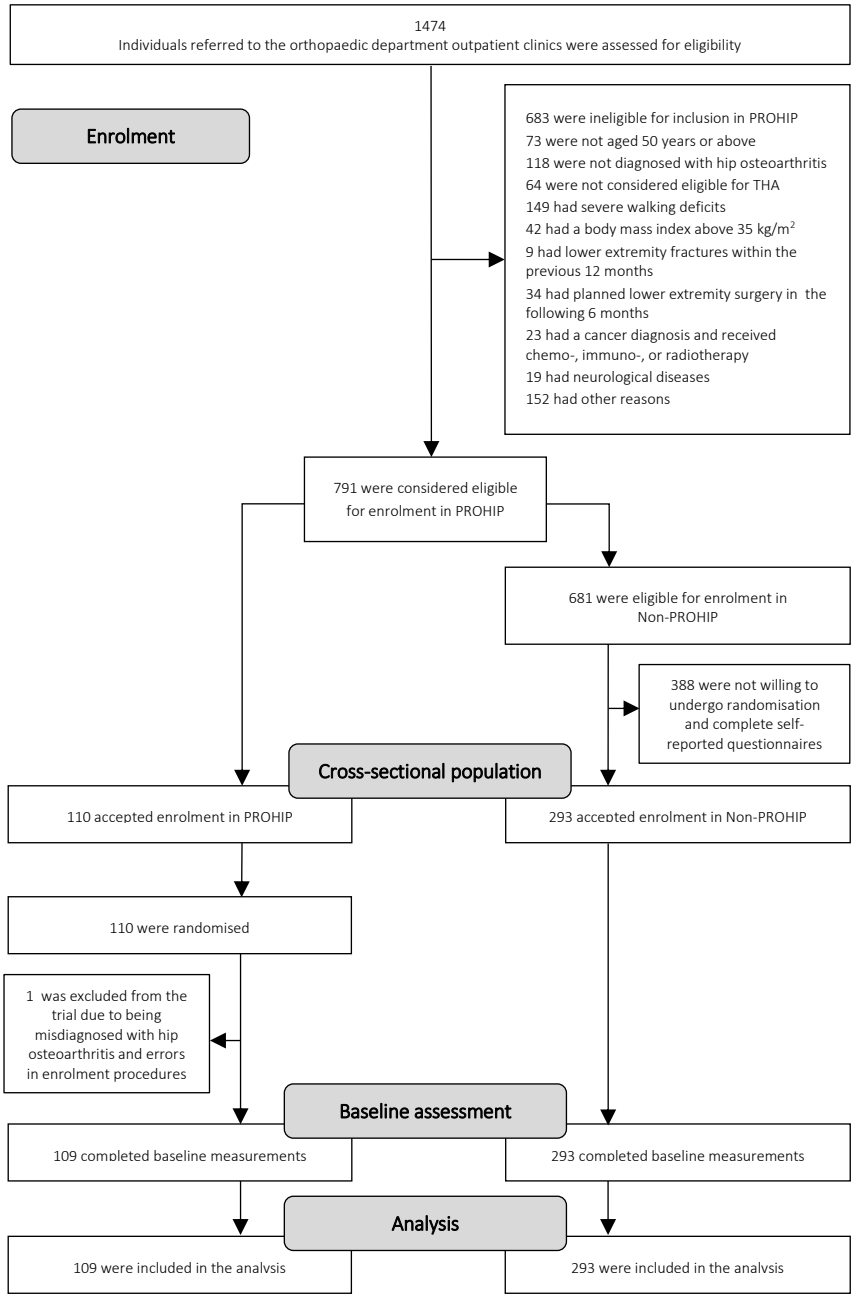


Figure 19. Flow of participants in this cross sectional study. PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial. Parallel observational cohort (Non-PROHIP). Total hip arthroplasty (THA). This figure is reused from the manuscripts for *Study III*.

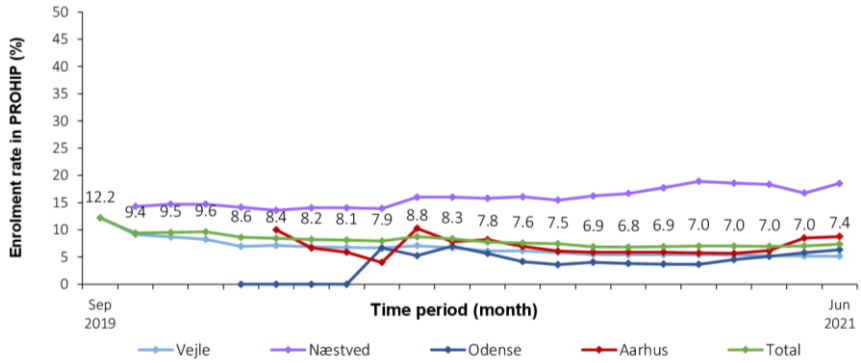


Figure 20. Enrolment rate in the PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial. This figure is reused from the manuscript for *Study III*.

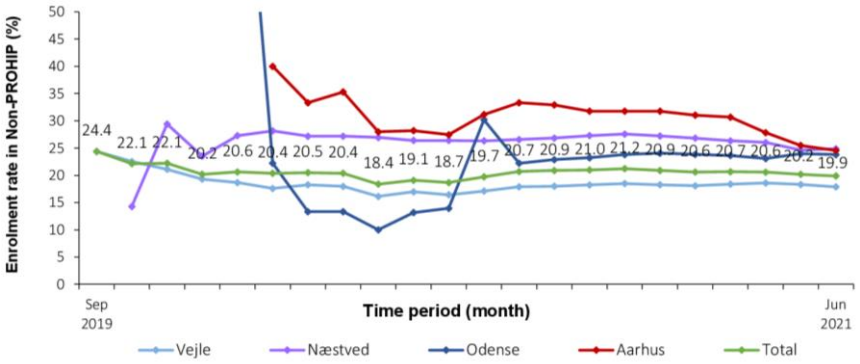


Figure 21. Enrolment rate in the parallel observational cohort (Non-PROHIP). This figure is reused from the manuscript for *Study III*.

Self-reported characteristics

Participants in the PROHIP group had a higher body mass index than participants in the Non-PROHIP group at baseline (group difference 1.4 kg/m2 [95% CI 0.5 to 2.3], STDdiff=0.36, P=0.002). A lower proportion of the participants in the PROHIP group had previously received a THA on the opposite side of the affected hip (group difference -13.5% points [95% CI -20.9 to -6.0], STDdiff=0.37, P=0.002) or TKA on either side (group difference -6.4% points [95% CI -10.4 to -2.3], STDdiff=0.29, P=0.021) or had attended supervised exercise (group difference -10.8% points [95% CI -21.0 to -0.7], STDdiff=0.23, P=0.048) compared with participants in the Non-PROHIP group at baseline. There were no differences between the two groups in the remaining self-reported baseline characteristics (**Table 11**).

Table 11. Self-reported baseline characteristics of participants enrolled in the randomised controlled trial (PROHIP) and parallel prospective observational cohort (non-PROHIP).‡ This table is reused from the manuscript for *Study III*.

Self-reported characteristic variables	Baseline values		Between-Group Difference	
	PROHIP (N=109)	Non-PROHIP (N=293)¤	Crude Mean Difference (95% CI)	STDdiff
Female sex, n (%)	54 (49.5)	147 (50.1)	-0.6 (-11.6 to 10.4)	0.01
Age, years	67.6 (7.2)	68.2 (7.9)	-0.6 (-2.3 to 1.1)	0.08
Height, m¤	1.71 (0.09)	1.73 (0.08)	-0.02 (-0.04 to -0.00)	0.24
Weight, kg¤	81.9 (14.2)	79.8 (15.1)	2.1 (-1.2 to 5.4)	0.14
Body mass index, kg/m²¤	28.1 (3.8)	26.7 (4.0)	1.4 (0.5 to 2.3)*	0.36
Education level above high school, n (%)	57 (52.3)	163 (55.6)	-3.3 (-14.3 to 7.6)	0.07
Employment, n (%)				
Employed for wages or self-employed	35 (32.1)	96 (32.8)	-0.7 (-10.9 to 9.6)	0.01
Sick leave	3 (2.8)	5 (1.7)	1.1 (-2.4 to 4.5)	0.07
Retired	70 (64.2)	179 (61.1)	3.1 (-7.5 to 13.7)	0.06
Other status	1 (0.9)	13 (4.4)	-3.5 (-6.5 to -0.6)	0.22
Current smoker, n (%)	5 (4.6)	30 (10.2)	-5.6 (-10.9 to -0.4)	0.22
Alcohol intake above 10 units per week, n (%)	13 (11.9)	22 (7.5)	4.4 (-2.4 to 11.2)	0.15
Affected hip at right side, n (%)	62 (56.9)	150 (51.2)	5.7 (-5.2 to 16.6)	0.11
Duration of hip symptoms, years	2.3 (2.1)	2.3 (2.8)	0.0 (-0.6 to 0.6)	0.00
Previous total hip arthroplasty, n (%)	11 (10.1)	69 (23.6)	-13.5 (-20.9 to -6.0)*	0.37
Previous total knee arthroplasty, n (%)	2 (1.8)	24 (8.2)	-6.4 (-10.4 to -2.3)*	0.29
Previous treatment due to hip symptoms, n (%)				
Supervised exercise	31 (28.4)	115 (39.6)	-10.8 (-21.0 to -0.7)*	0.23
Manual and/or passive treatment	17 (15.6)	64 (21.8)	-6.2 (-14.5 to 2.0)	0.16
Corticosteroid injection	3 (2.8)	22 (7.5)	-4.7 (-9.1 to -0.5)	0.22
Other non-surgical treatment	13 (11.9)	58 (19.8)	-7.9 (-15.5 to -0.3)	0.22
Use of analgesics due to hip-related pain, n (%)				
Paracetamol	83 (76.1)	234 (79.9)	-3.7 (-12.9 to 5.5)	0.09
Non-steroidal anti-inflammatory drugs	39 (35.8)	88 (30.0)	5.8 (-4.7 to 16.2)	0.12
Morphine or opioids	8 (7.3)	21 (7.2)	0.1 (-5.6 to 5.9)	0.01
Other analgesic	9 (8.3)	19 (6.5)	1.8 (-4.1 to 7.7)	0.07
Comorbidities, n (%)				
None	55 (50.4)	144 (49.1)	1.3 (-9.7 to 12.3)	0.03
1	20 (18.4)	62 (21.2)	-2.8 (-11.5 to 5.8)	0.07
2	17 (15.6)	52 (17.8)	-2.2 (-10.2 to 5.9)	0.06
3 or more	17 (15.6)	35 (11.9)	3.7 (-4.1 to 11.4)	0.11

‡ Plus-minus values are means (±standard deviation) unless otherwise indicated; ¤ In non-PROHIP, 4 participants had missing data on height, weight, and body mass index; * Denotes *P*-value <0.05 from Fisher's Exact Test for dichotomous variables and Wilcoxon Rank-sum Test for continuous variables; Standardised difference (STDdiff).

Primary outcome variable

The mean score (SD) in the OHS was 25.1 (5.9) in the PROHIP group and 22.6 (6.9) in the Non-PROHIP at baseline, with a group difference of 2.5

points (95% CI 1.1 to 4.0, STDdiff=0.39, P<0.001). This corresponded to a statistically significant difference above the threshold for a potential imbalance between the groups when comparing the distributions of the baseline scores, but it was not considered clinically significant as the upper limit of 95% CI was below the MID (**Table 12**).

Key secondary outcome variables

Participants in the PROHIP group had better mean scores in HOOS pain (group difference of 4.9 points [95% CI 1.4 to 8.3], STDdiff=0.31, P=0.016), HOOS symptoms (group difference of 5.6 points [95% CI 1.9 to 9.3], STDdiff=0.33, P=0.001), HOOS function in activities of daily living (group difference of 7.4 points [95% CI 3.5 to 11.3], STDdiff=0.42, P<0.001), HOOS function in sports and recreation (group difference of 8.1 points [95% CI 4.0 to 12.3], STDdiff=0.43, P<0.001), and HOOS hip-related quality of life (group difference of 7.7 points [95% CI 4.4 to 11.0], STDdiff=0.51, P<0.001) in comparison to the participants in the Non-PROHIP group, while there was no difference in the UCLA activity score between the two groups at baseline (group difference of 0.2 points [95% CI -0.2 to 0.6], STDdiff=0.12, P=0.253). The group differences in the five HOOS subscales were statistically significant and above the threshold for a potential imbalance between the groups when comparing the distributions of the baseline scores. For the HOOS function in activities of daily living, function in sports and recreation, and hip-related quality of life subscales, these differences between the two groups were considered possibly clinical significant as the 95% CI included the MID (**Table 12**).

Other outcome variables

Participants in the PROHIP group had better mean scores in VAS hip pain at rest (group difference of -9.1 points [95% CI -14.2 to -4.0], STDdiff=0.39, P<0.001), VAS hip pain during activities (group difference of -6.3 points [95% CI -10.0 to -2.7], STDdiff=0.38, P<0.001), EQ-5D-5L index score (group difference of 0.099 points [95% CI 0.041 to 0.156], STDdiff=0.40, P=0.001), and EQ-VAS (group difference of 7.5 points [95% CI 2.6 to 12.5], STDdiff=0.34, P=0.003) than participants in the Non-PROHIP group at

baseline. All these group differences were statistically significant and above the threshold for a potential imbalance between the groups when comparing the distributions of the baseline scores. For the EQ-VAS, the difference between the two groups was considered possibly clinical significant as the 95% CI included the MID (**Table 12**).

Table 12. Self-reported outcome scores of participants enrolled in the randomised controlled trial (PROHIP) and parallel prospective observational cohort (Non-PROHIP) at baseline.‡ This table is reused from the manuscript for *Study III*.

Self-reported outcome variables	Baseline scores		Between-Group Difference	
	PROHIP (N=109)	Non-PROHIP (N=293)	Crude Mean Difference (95% CI)	STDdiff
Primary outcome				
OHS, 0 to 48	25.1 (5.9)	22.6 (6.9)	2.5 (1.1 to 4.0)*	0.39
Key secondary outcomes				
HOOS subscales, 0 to 100				
Pain	47.8 (15.0)	42.9 (15.9)	4.9 (1.4 to 8.3)*	0.31
Symptoms	45.8 (17.7)	40.2 (16.4)	5.6 (1.9 to 9.3)*	0.33
ADL	54.1 (17.4)	46.7 (17.9)	7.4 (3.5 to 11.3)*	0.42
Sport/rec	31.5 (19.8)	23.4 (18.1)	8.1 (4.0 to 12.2)*	0.43
QoL	34.0 (15.4)	26.3 (14.7)	7.7 (4.4 to 11.0)*	0.51
UCLA activity score, 1 to 10	5.2 (1.7)	5.0 (2.0)	0.2 (-0.2 to 0.6)	0.12
Other outcomes				
VAS hip pain at rest, 0 to 100	41.5 (22.5)	50.6 (23.6)	-9.1 (-14.2 to -4.0)*	0.39
VAS hip pain during activity, 0 to 100	64.8 (16.4)	71.1 (16.5)	-6.3 (-10.0 to -2.7)*	0.38
EQ-5D-5L index score, -0.757 to 1.000	0.674 (0.225)	0.575 (0.273)	0.099 (0.041 to 0.156)*	0.40
EQ-VAS, 0 to 100	60.4 (21.5)	52.9 (22.7)	7.5 (2.6 to 12.5)*	0.34

‡ Plus-minus values are means (±standard deviation) unless otherwise indicated; * Denotes *P*-value <0.05 from Wilcoxon Rank-sum Test; Standardised difference (STDdiff); The Oxford Hip Score (OHS) ranges from 0 (worst) to 48 (best); The Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (Sport/rec), and hip-related quality of life (QoL) range from 0 (worst) to 100 (best); The University of California Los Angeles (UCLA) activity score ranges from 1 (worst) to 10 (best); The Visual Analogue Scale (VAS) ranges from 0 (best) to 100 (worst); The EuroQol Group 5-dimensions 5-levels (EQ-5D-5L) index score ranges from -0.757 (worst) to 1.000 (best); The EuroQol Group Visual Analogue Scale (EQ-VAS) ranges 0 (worst) to 100 (best).

Factors related to accepting enrolment in the randomised controlled trial

Participants with better scores on the OHS, HOOS subscales, EQ-5D-5L index score, and EQ-VAS and higher body mass index at baseline had increased odds of accepting enrolment in PROHIP. In contrary, participants who previously had received a THA, TKA or supervised exercise and worse baseline scores on the VAS hip pain at rest and during activities had decreased odds of accepting enrolment in PROHIP (**Table 13**).

Table 13. Odds of accepting enrolment in the PROgressive resistance training versus total hip arthroplasty (PROHIP) trial depending on self-reported characteristics and outcome scores at baseline. This table is reused from the manuscript for *Study III*.

Baseline characteristic and outcome variables	Univariate logistic regression estimates		
	Odds ratio	95% CI	*P*-value
Female sex	0.98	0.63 to 1.51	0.911
Age	0.99	0.96 to 1.02	0.472
Height‡	0.97	0.95 to 1.00	0.033
Weight‡	1.01	0.99 to 1.02	0.211
Body mass index‡	1.09	1.03 to 1.15	0.002
Education level above high school	0.87	0.56 to 1.36	0.550
Employment			
Employed for wages or self-employed	0.97	0.61 to 1.55	0.901
Sick leave	1.63	0.38 to 6.94	0.508
Retired	1.14	0.72 to 1.80	0.566
Other status	0.20	0.03 to 1.54	0.122
Current smoker	0.42	0.16 to 1.12	0.082
Alcohol intake above 10 units per week	1.66	0.81 to 3.44	0.166
Affected hip at right side	1.26	0.81 to 1.96	0.310
Duration of hip symptoms	1.00	0.92 to 1.09	0.995
Previous total hip arthroplasty	0.36	0.18 to 0.72	0.004
Previous total knee arthroplasty	0.21	0.05 to 0.90	0.036
Previous treatment due to hip symptoms			
Supervised exercise	0.62	0.39 to 0.99	0.046
Manual and/or passive treatment	0.66	0.37 to 1.19	0.167
Corticosteroid injection	0.35	0.10 to 1.19	0.092
Other non-surgical treatment	0.55	0.29 to 1.05	0.069
Use of analgesics due to hip-related pain			
Paracetamol	0.80	0.48 to 1.36	0.418
Non-steroidal anti-inflammatory drugs	1.29	0.82 to 2.07	0.271
Morphine or opioids	1.03	0.44 to 2.29	0.953
Other analgesic	1.30	0.57 to 2.96	0.536
Comorbidities			
None	1.05	0.68 to 1.64	0.815
1	0.84	0.48 to 1.47	0.534
2	0.86	0.47 to 1.56	0.611
3 or more	1.36	0.73 to 2.55	0.334
OHS	1.06	1.02 to 1.10	0.001
HOOS subscales			
Pain	1.02	1.01 to 1.03	0.007
Symptoms	1.02	1.01 to 1.03	0.003
ADL	1.02	1.01 to 1.04	<0.001
Sport/rec	1.02	1.01 to 1.03	<0.001
QoL	1.03	1.02 to 1.05	<0.001
UCLA activity score	1.06	0.95 to 1.19	0.303
VAS hip pain at rest	0.98	0.97 to 0.99	0.001
VAS hip pain during activity	0.97	0.97 to 0.99	0.001
EQ-5D-5L index score	1.02	1.01 to 1.03	0.001
EQ-VAS	1.02	1.01 to 1.03	0.003

‡ 4 participants had missing data on height, weight, and body mass index; The Oxford Hip Score (OHS); The Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (sport/rec), and hip-related quality of life (QoL); The University of California Los Angeles (UCLA) activity score; The Visual Analogue Scale (VAS); The EuroQol Group 5-dimensions 5-levels (EQ-5D-5L); The EuroQol Group Visual Analogue Scale (EQ-VAS).

Total hip arthroplasty versus progressive resistance training

Study IV

Enrolment, participant characteristics and treatment adherence

In total, 1474 individuals referred to the orthopaedic department outpatient clinics were assessed for eligibility. This yielded that 791 (53.7%) were deemed eligible for enrolment, and 109 (7.4%) were randomly allocated. Out of these, 50 of 53 (94.3%) assigned to the THA group and 53 of 56 assigned to the PRT group (94.6%) completed the trial at 6 months follow-up. Of the 53 participants randomly allocated to the THA group, 5 (9.4%) decided not to undergo surgery. Of the 56 participants randomly allocated to the PRT group, 12 (21.4%) received THA surgery during the 6 months follow-up (**Figure 22**).

The mean (SD) age of participants was 67.6 (7.2) years, 54 (49.5%) were female, 57 (52.3%) had an educational level beyond high school, 70 (64.2%) were retired, and the median hip symptom duration (IQR) was 1.7 (1.0; 3.0) years. Baseline characteristics were similar in the two groups, except for a potentially larger proportion in the PRT group who previously had received a THA in the contralateral side of the affected hip (**Table 14**).

Treatment adherence was generally satisfactory across both groups. In the THA group, 48 (90.6%) participants received surgery. In the PRT group, participants attended an average of 20.6 (85.7%) out of 24 supervised training sessions, with 47 (83.9%) participants attending 18 or more training sessions.

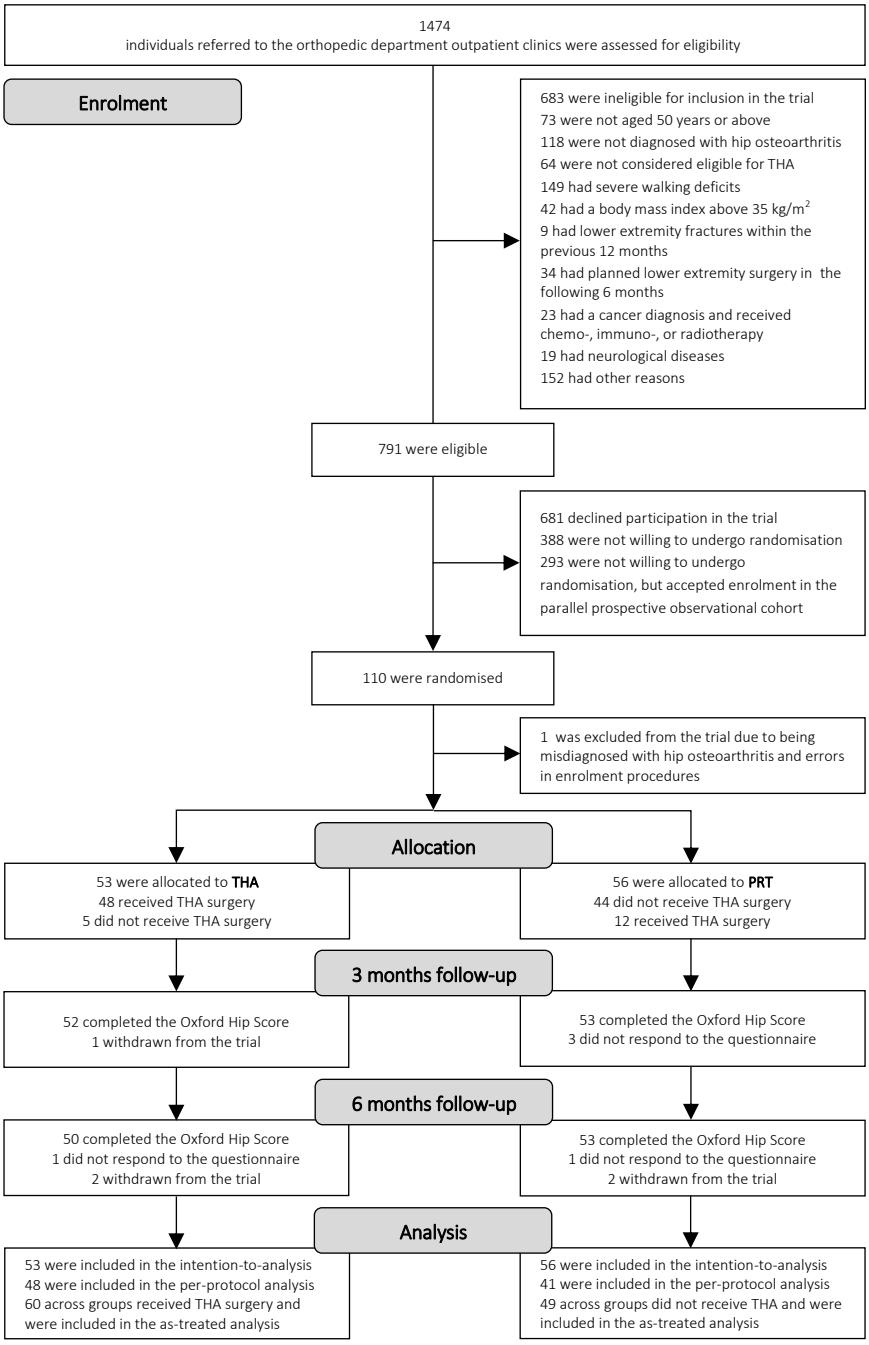


Figure 22. Flow of participants in this randomised controlled trial. Total hip arthroplasty (THA). Progressive resistance training (PRT). This figure is reused from the manuscript for *Study IV*.

Table 14. Baseline characteristics of the participants in the intention-to-treat population.‡ This table is reused from the manuscript for *Study IV*.

Baseline characteristic variables	THA (N=53)	PRT (N=56)	Total (N=109)
Female sex, n (%)	26 (49.1)	28 (50.0)	54 (49.5)
Age, years	67.5 (7.3)	67.6 (7.1)	67.6 (7.2)
Height, m	1.70 (0.08)	1.71 (0.09)	1.71 (0.09)
Weight, kg	81.0 (13.4)	82.8 (14.9)	81.9 (14.2)
Body mass index, kg/m^2	27.9 (3.9)	28.2 (3.8)	28.1 (3.8)
Education level above high school, n (%)	29 (54.7)	28 (50.0)	57 (52.3)
Employment, n (%)			
Employed for wages or self-employed	19 (35.8)	16 (28.6)	35 (32.1)
Sick leave	32 (60.4)	38 (67.9)	3 (2.8)
Retired	1 (1.9)	2 (3.6)	70 (64.2)
Other status	1 (1.9)	0 (0.0)	1 (0.9)
Current smoker, n (%)	1 (1.9)	4 (7.1)	5 (4.6)
Alcohol intake above 10 units per week, n (%)	6 (11.3)	7 (12.5)	13 (11.9)
Affected hip at right side, n (%)	29 (54.7)	33 (58.9)	62 (56.9)
Duration of hip symptoms, years, median (IQR)	2.0 (1.0; 3.0)	1.5 (0.7; 4.0)	1.7 (1.0; 3.0)
Previous total hip arthroplasty, n (%)	2 (3.8)	9 (16.1)	11 (10.1)
Previous total knee arthroplasty, n (%)	1 (1.9)	1 (1.9)	2 (1.8)
Use of analgesics due to hip-related pain, n (%)			
Paracetamol	38 (71.7)	45 (80.4)	83 (76.1)
Non-steroidal anti-inflammatory drugs	22 (41.5)	17 (30.4)	39 (35.8)
Morphine or opioids	5 (9.4)	3 (5.4)	8 (7.3)
Other analgesic	5 (9.4)	4 (7.1)	9 (8.3)
OHS, 0 to 48	25.4 (6.2)	24.8 (5.6)	25.1 (5.9)
HOOS subscales, 0 to 100			
Pain	49.7 (13.4)	46.0 (16.3)	47.8 (15.0)
Symptoms	47.7 (18.5)	44.0 (16.8)	45.8 (17.7)
ADL	55.8 (17.1)	52.5 (17.7)	54.1 (17.4)
Sport/rec	32.0 (19.3)	31.1 (20.4)	31.5 (19.8)
QoL	34.0 (16.0)	34.0 (15.0)	34.0 (15.4)
UCLA activity score, 1 to 10	5.3 (1.8)	5.1 (1.7)	5.2 (1.7)
40m-FPWT, m/s	1.5 (0.3)	1.4 (0.3)	1.5 (0.3)
30s-CST, number of chair stands	11.1 (3.6)	10.6 (3.4)	10.8 (3.5)

‡ Plus-minus values are means ± (standard deviation) unless otherwise indicated; Total Hip Arthroplasty (THA); Progressive Resistance Training (PRT); The Oxford Hip Score (OHS) ranges from 0 (worst) to 48 (best); The Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (Sport/rec), and hip-related quality of life (QoL) range from 0 (worst) to 100 (best); The University of California Los Angeles (UCLA) activity score ranges from 1 (worst) to 10 (best); The 40-meter Fast Paced Walk Test (40m-FPWT) measures gait speed in meters/second; and 30-second Chair Stand Test (30s-CST) measures the total number of completed chair stands in 30 seconds.

Primary outcome

The mean changes (SE) in the OHS were 15.9 (1.0) in the THA group and 4.5 (1.0) in the PRT group from baseline to 6 months follow-up (**Figure 23**). This corresponded to a statistically and clinically significant greater improvement in the OHS in the THA group compared with the PRT group, with a mean difference between the two groups of 11.4 points (95% CI 8.9 to 11.4, P<0.001). The number (%) of participants that improved in accordance with the OHS MIC responder criteria were 40 (75.5%) in the THA group and 21 (37.5%) in the PRT group, with a RD between the two groups of 0.38 (95% CI 0.21 to 0.55). The number (%) of participants that were classified as treatment responders in accordance with the OMERACT-OARSI responder criteria were 41 (77.4%) in the THA group and 21 (37.5%) in the PRT group, with a RD between the two groups of 0.40 (95% CI 0.23 to 0.57) (**Table 15**).

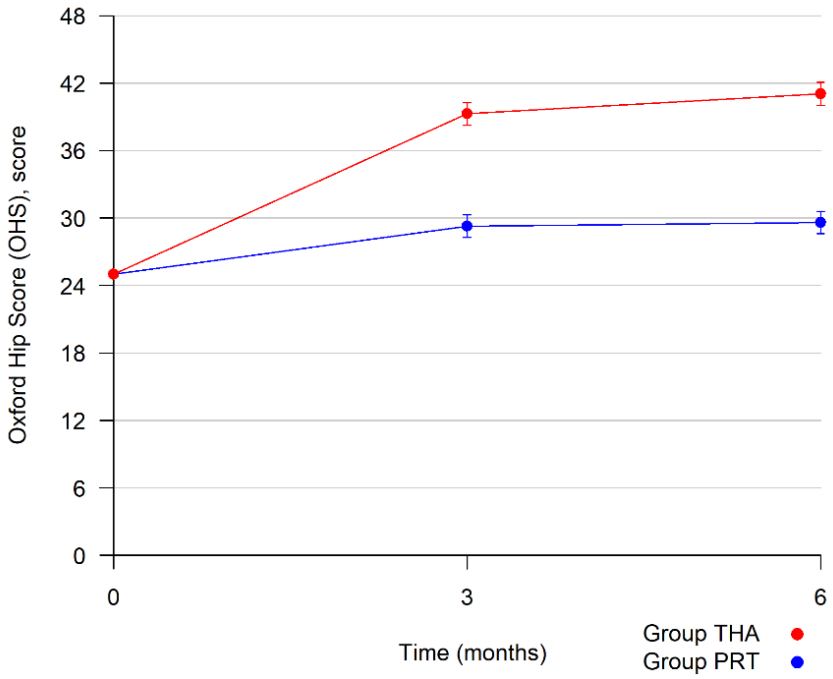


Figure 23. Trajectory in the Oxford Hip Score (OHS) in the total hip arthroplasty (THA) group and progressive resistance training (PRT) group from baseline to 6 months follow-up. Values are means and standard errors. This figure is reused from the manuscript for *Study IV*.

Key secondary outcomes

At 6 months follow-up, the THA group also displayed statistically and clinically significant larger improvements in each of the five HOOS subscales in comparison to the PRT group, with mean group differences of 24.2 points (95% CI 18.2 to 30.2, P<0.001) for HOOS pain, 25.7 points (95% CI 19.5 to 31.8, P<0.001) for HOOS symptoms, 20.8 points (95% CI 15.2 to 26.3, P<0.001) for HOOS function in activities of daily living, 32.7 points (95% CI 25.0 to 40.4, P<0.001) for HOOS function in sports and recreation, and 31.8 points (95% CI 24.9 to 38.8, P<0.001) for HOOS quality of life. The THA group showed statistically, but not clinically better improvements in the UCLA activity score and 40m-FPWT than the PRT group at 6 months follow-up, with a mean group difference of 0.7 points (95% CI 0.1 to 1.3, P=0.018) and median group difference of 0.10 m/s (95% 0.03 to 0.17, P=0.009), respectively. There was no difference between the groups in the 30s-CST at 6 months follow-up, with a median group difference of 0.0 repetitions (95% CI -1.0 to 2.0, P=0.361) (**Table 15**).

Serious adverse events

During the 6 months follow-up, SAEs occurred in 11 (10.1%) participants, with 6 (11.3%) in the THA group and 5 (8.9%) in the PRT group. In the PRT group, hip dislocation led to discontinuation in the trial from one participant, but this event occurred after the participant had crossed over to THA surgery (**Table 16**).

Sensitivity analyses

The per-protocol, single-step non-responder imputation, and as-treated analyses yielded similar results as the intention-to-treat analysis, with group differences in favour of THA in the primary outcome and most of the key secondary outcomes at 6 months follow-up, indicating robust estimates. In the as-treated analysis, participants randomly allocated to THA who did not undergo surgery had similar improvements in the primary and most key secondary outcomes compared with those randomly allocated to THA and PRT who received surgery (**Appendix 7**).

Table 15. Outcomes in the intention-to-treat population at 6 months follow-up.‡ This table is reused from the manuscript for *Study IV*.

Outcomes	Change from Baseline to 6 months follow-up		Between-Group Difference in Mean Improvement	
	THA (N=53)	PRT (N=56)	Adjusted Mean Difference (95% CI)	*P*-value
Primary outcome				
OHS, 0 to 48	15.9 (1.0)	4.5 (1.0)	11.4 (8.9 to 14.0)	<0.001
Key secondary outcomes				
HOOS subscales, 0 to 100				
Pain	39.2 (2.4)	15.0 (2.3)	24.2 (18.2 to 30.2)	<0.001
Symptoms	39.3 (2.5)	13.6 (2.36)	25.7 (19.5 to 31.8)	<0.001
ADL	32.9 (2.2)	12.1 (2.13)	20.8 (15.2 to 26.3)	<0.001
Sport/rec	43.5 (3.1)	10.7 (3.0)	32.7 (25.0 to 40.4)	<0.001
QoL	41.0 (2.8)	9.2 (2.7)	31.8 (24.9 to 38.8)	<0.001
UCLA activity score, 1 to 10	1.2 (0.2)	0.5 (0.2)	0.7 (0.1 to 1.3)	0.018
40m-FPWT, m/s‡	0.15 (0.05; 0.33)	0.06 (-0.05; 0.19)	0.10 (0.03 to 0.17)	0.009
30s-CST, number of chair stands‡	1.00 (0.0; 4.0)	1.0 (0.0; 3.0)	0.0 (-1.0 to 2.0)	0.361
Response to Treatment				
OHS MIC criteria, n (%)	40 (75.5)	21 (37.5)	0.38 (0.21 to 0.55)	
OMERACT-OARSI criteria, n (%)	41 (77.4)	21 (37.5)	0.40 (0.23 to 0.57)	

‡ All analyses was based on the intention-to-treat population. For continues outcomes, repeated measures linear mixed effects models (with no imputation for missing data) were used for estimating least squares means and standard errors, and mean differences between groups were reported with 95% confidence intervals. For dichotomous outcomes, n (%) and risk differences were estimated with corresponding 95% confidence intervals using a conservative non-responder imputation; ǂ Median (IQR) and median differences with 95% confidence intervals were reported for these outcomes (with no imputation for missing data). For both outcomes, there were missing data in 4 participants in the THA group and in 5 participants in the PRT group; Total Hip Arthroplasty (THA); Progressive Resistance Training (PRT); The Oxford Hip Score (OHS) ranges from 0 (worst) to 48 (best); The Hip disability Osteoarthritis Outcome Score (HOOS) subscales covering pain, symptoms, function in activities of daily living (ADL), function in sports and recreation (Sport/rec), and hip-related quality of life (QoL) range from 0 (worst) to 100 (best); The University of California Los Angeles (UCLA) activity score ranges from 1 (worst) to 10 (best); The 40-meter Fast Paced Walk Test (40m-FPWT) measures gait speed in meters/second; and 30-second Chair Stand Test (30s-CST) measures the total number of completed chair stands in 30 seconds; In the OHS minimal important change (MIC) criteria, participants were classified as responders if the OHS improved by at least 8 points; In the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) criteria, participants were classified as responders if the OHS pain or function subscales improved by 50% or more and by 20 points or more; or if two of the following three criteria were met: the OHS pain subscale improved by 20% or more and by 10 points or more; the OHS function subscale improved by 20% or more and by 10 points or more, or the OHS sum score improved by 20% or more and by 10 points or more. The OHS includes two subscales for pain and function ranging from 0 (worst) to 100 (best).

Table 16. Serious adverse events in the intention-to-treat population at 6 months follow-up.‡ This table is reused from *Study IV*.

Serious adverse event	THA (N=53)	PRT (N=56)	Total (N=109)
Musculoskeletal			
Prosthetic joint infection	1 (1.9)	0 (0)	1 (0.9)
Hip dislocation	1 (1.9)	1 (1.8)†	2 (1.8)
Periprosthetic fracture	0 (0.0)	0 (0.0)	0 (0.0)
Aseptic loosening	0 (0.0)	0 (0.0)	0 (0.0)
Revision surgery	2 (3.8)	0 (0.0)	2 (1.8)
Pelvic and distal radius fractures	0 (0.0)	1 (1.8)‡	1 (0.9)
Total shoulder arthroplasty surgery	0 (0.0)	1 (1.8)§	1 (0.9)
Cardiovascular			
Vascular injury	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)
Deep venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (1.8)¶	1 (0.9)
Nervous system			
Drop foot	1 (1.9)	0 (0.0)	1 (0.9)
Gastrointestinal			
Reflux	1 (1.9)	0 (0.0)	1 (0.9)
Renal			
Urinary tract and kidney infection	0 (0.0)	1 (1.8)	1 (0.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to serious adverse event	0 (0.0)	1 (1.8)	1 (0.9)
Total serious adverse events	6 (11.3)	5 (8.9)	11 (10.1)

‡ Serious adverse events that occurred from baseline to 6 months follow-up, but which not necessarily had a causal relationship with the treatments were reported with n (%). All serious adverse events were adjudicated for severity in accordance with the definitions from the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines (i.e., any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability or impairment, and resulted in congenital anomaly or birth defect); Total Hip Arthroplasty (THA); Progressive Resistance Training (PRT); † This event occurred after the participant had crossed over and received THA, and led to discontinuation in the trial; ‡ This event occurred in a participant as a result from a fall during a leisure time activity; § This event occurred in a participant with known long-term shoulder complaints; ¶ This event occurred after the participant had crossed over and received THA.

Discussion

Summary of main findings

Study I

This qualitative patient and public involvement study displayed that patient stakeholders with severe hip pain and symptoms perceived themselves as highly disabled and considered treatment without THA surgery unlikely. Patient stakeholders also expected a fast recovery with complete reduction of hip pain, restored functional performance, and return to desired activities of daily living after THA surgery, whereas more uncertainty and scepticism about the potential benefits of exercise were highlighted. All key stakeholders, apart from the physiotherapists, considered exercise as most suitable in the management of mild to moderate hip OA or as a supplement treatment to THA surgery. Orthopaedic surgeons and physiotherapist tended to deliver information about management options including relative treatment effectiveness that were tailored to their favoured treatment. Several facilitators and barriers for THA surgery and exercise were identified, and the main included patient age, pain management without analgesics, risk of serious adverse events, perception of improvement, diagnostic imaging, supervision, and habitualised exercise. Patients and clinician stakeholders highlighted improvement in hip pain and hip function as the two most important outcomes in order to assess the effectiveness of either THA surgery or exercise. Based on these findings, several methodological considerations and strategies were implemented into the trial protocol. Mainly, these comprised inclusion of a parallel prospective observational cohort to provide an indication of the generalisability of the randomised controlled trial, development of an enrolment procedure using generic guidance delivered by an independent clinician to reduce disclosures of personal opinions and facilitate communication of clinical equipoise, and selection of change in hip pain and function as the primary outcome.

Study II

A protocol for a high quality open-label, multicentre, parallel-group, randomised (1:1 allocation ratio, electronic concealment, and varying block sizes) controlled superiority trial comparing THA surgery with a PRT programme in individuals with hip OA was designed and described. This protocol included detailed descriptions and pre-specified considerations about study design, inclusion and exclusion criteria, enrolment procedures, randomisation and allocation concealment, blinding, parallel prospective observational cohort for eligible individuals who declined participation in the randomised trial, interventions, definition of primary and key secondary outcomes, data collection, sample size and power calculation, and statistical methods.

Study III

This cross-sectional study showed that individuals with hip OA enrolled in the randomised controlled trial had different self-reported characteristics and outcome scores at baseline than those in the parallel observational cohort. Participants in the randomised trial reported less hip pain and impaired function, and less impairments in individual domains of pain, symptoms, physical function, quality of life and overall health status, had higher body mass index, and fewer had previously received total joint arthroplasty surgery or attended supervised exercise. All between-group differences in self-reported outcome scores were small to moderate and only considered possibly clinically significant for individual domains of physical function, hip-related quality of life and overall health status. Better self-reported outcome scores on the OHS, HOOS subscales, EQ-5D index score, and EQ-VAS as well as higher body mass index at baseline were associated with increased odds of accepting enrolment in the randomised controlled trial, whereas worse baseline scores on the VAS and previous THA, TKA or supervised exercise were associated with decreased odds. These findings may represent an indication of limited generalisability of the randomised controlled trial.

Study IV

Among individuals aged 50 years or above with severe hip OA considered eligible for surgery, THA offered clinically significant superior improvements in self-reported hip pain and function compared with PRT at 6 months follow-up. Furthermore, THA also provided clinically significant greater improvements in individual domains of self-reported pain, symptoms, physical function and quality of life, and led to statistically, but not clinically significant, larger improvements in self-reported physical activity level and functional performance in gait function, whereas it provided no additional improvement in performance-based sit-to-stand function compared with PRT. About 75% assigned to receive THA surgery experienced clinically important improvements in self-reported hip pain and function in comparison to 37% assigned to receive PRT. The frequency of SAEs were similar between the two groups.

Interpretation of findings and comparison with previous studies

Study I

In accordance with the current findings, a recent qualitative study also demonstrated clear and high expectations for THA or TKA surgery among Swedish individuals with knee or hip OA.[178] However, numerous individuals reconsidered their treatment options as well as changed attitudes towards either undergoing or refusing surgery after completion of a digital non-surgical treatment program.[178] This highlights the importance of delivering appropriate information about treatment options to facilitate shared-decision making in the management of hip OA. The current findings also indicated that patient stakeholders exhibited uncertainty and scepticism about the potential benefits of exercise such as PRT. These perceptions may originate from uncertainties and lack of knowledge about the effectiveness of exercise amongst orthopaedic surgeons and physiotherapists,[179] and limited experience with exercise amongst individuals with hip, as less than 40% are recommended or referred to exercise as part of the first-line non-surgical management.[180] Based on findings from previous qualitative studies,[181] [182] recovery expectations among patient stakeholders in this

study appeared related to the criteria of resolution for THA surgery and redefinition for PRT. This may indicate that individuals who accept enrolment in the randomised controlled trial may differ from those who decline enrolment in terms of recovery expectations, hip pain and functional disability, highlighting decreased generalisability to clinical practice as a potential limitation of the trial.

The current findings indicated that orthopaedic surgeons and physiotherapists tended to deliver information about management that were tailored to their favoured treatment. This strategy is in disparity to the information needs desired by individuals with hip OA during medical consultations,[183] and since clinicians have a substantial impact on the attitudes and beliefs of patients this may result in misconceptions and uninformed decisions.[183 184] In the context of the randomised controlled trial, this indicate that both orthopaedic surgeons and physiotherapists could influence patient opinions about THA surgery and PRT in either direction during enrolment procedures by emphasising the benefits of their favoured treatment option, while simultaneously highlighting the limitations of the other treatment option. This may increase the risk of selection bias, and thus emphasise that detailed verbal information about the randomised trial should be delivered by an independent clinician group during enrolment procedures in order to reduce this potential bias.

Clinician stakeholders in this study demonstrated conflicting opinions on the indication criteria for THA, in line with findings across previous studies.[87 88 185-187] Even more interestingly, patient stakeholders believed findings or progression of hip OA on radiographic imaging to be the primary determining factor for THA surgery, even though there is low agreement between hip pain and radiographically verified hip OA.[50] This indicate that the patient stakeholders in this study displayed an outdated 'wear-and-tear' conception of hip OA that contradicts up-to-date insights on pathogenesis, in which it is considered as a whole-joint disease.[2] This misconception of hip OA is likely to be facilitated by clinician language and explanations.[188] These findings highlight the need of using neutral and evidence based information about THA and PRT during enrolment

procedures in the randomised controlled trial to decrease potential misconceptions among individuals with hip OA.

In line with the OMERACT-OARSI recommendations,[189-191] the current findings highlighted change in hip pain and function as the most important outcomes. A number of patient-reported outcome measures such as the OHS and HOOS are available to assess hip pain and function in individuals with hip OA.[131 189] In this regard, the OHS has been indicated to have the best validated clinometric properties.[131] The OHS has also been properly translated, cross-culturally adapted and validated in Danish displaying similar qualities to the original English version,[135] while the HOOS only has been translated and cross-culturally adapted into Danish.[141] This suggests that the OHS is as an appropriate primary outcome measure to assess self-reported change in hip pain and function among Danish individuals with severe hip OA enrolled in the randomised controlled trial.

Study II

This trial protocol was developed and designed to address a knowledge gap in the management of hip OA using transparent, detailed, and state-of-the-art methods ensuring basis for a high-quality trial to support future implications for clinical practice.

The inclusion and exclusion criteria in the current trial protocol were largely based on those from a previous randomised comparing preoperative PRT with usual care in individuals with severe hip OA scheduled for THA.[75 192] One of the primary reasons for this was to ensure feasibility of the PRT programme in the current trial protocol, and to exclude those individuals where non-surgical treatment was considered unsuitable in line with clinical guideline recommendations.[45] The inclusion criterion that involved an age cut point of 50 years or above was chosen as it conforms to the diagnostic clinical criteria for hip OA developed by the ACR,[46] and to increase the probability of recruiting participants with similar age distributions as the general population undergoing THA surgery. In this context, about 94% of the individuals who receive a THA in Denmark are aged at least 50 years, with a mean age of 70 years for females and 68 years for males.[84] A major challenge was to develop an indication criteria for THA,

as there were no widespread consensus across healthcare systems and hospitals as well as among orthopaedic surgeons.[87 88 185-187] Therefore, the current indication criteria for THA used in the trial protocol were established through discussion until agreement between the PROHIP trial steering committee and orthopaedic surgeons from the four hospitals was reached.

The primary outcome and key secondary outcome measures selected in the current trial protocol adheres to the core domain outcome set for measurement in randomised controlled trials of hip OA developed by the OMERACT-OARSI.[191] The development and latest update of the OMERACT-OARSI core outcome set involved a comprehensive and transparent process, including a systematic review of the literature, a Delphi survey of stakeholders, and a face-to-face consensus meeting. The updated core outcome set consist of five mandatory domains to measure including pain, physical function, quality of life, patients' global assessment, and adverse events.[191] This adherence to the OMERACT-OARSI core outcome set in the current trial protocol ensured that the selected questionnaires and functional tests measures outcome domains that were relevant and meaningful to all key stakeholders in the management of hip OA, and improved consistency and comparability with other previous or future research studies. Furthermore, selection of the specific primary, key secondary and other outcome measures in the trial protocol was guided by the findings from the patient and public involvement study (*Study I*).

Selection of the primary end-point in the current trial protocol was based on numerous considerations. First, in previous randomised controlled trials comparing surgical procedures with non-surgical treatment that used primary endpoints of 12 and 24 months, crossover rates have varied between 26% and 39%.[95-99] Second, only minor differences are observed in self-reported pain and function outcome trajectories from 6 to 12 months after THA. Third, the improvements from exercise appear to diminish gradually after the supervised period has ended among individuals with hip OA, which may possibly be due to limited long-term adherence.[59] To reduce the risk of these factors that could possibly

affect the true difference between THA and PRT, the primary endpoint of 6 months after initiation of treatment was chosen in the current trial protocol.

Selection of the non-surgical treatment modality in the current trial protocol included some deliberations, since there was insufficient evidence in relation to recommendations on optimal type and dosage of exercise in the management of hip OA.[56 58 65 71] In this regard, the rationale for using PRT as a comparator to THA was based on that hip OA is associated with substantial atrophy and weakness of the hip and lower extremity muscles.[32-37] Furthermore, PRT is recommended for and maintaining and developing muscle strength in adults of all ages,[72 193] in addition to demonstrating clinically relevant improvements in hip pain, physical function, and quality of life even among individuals with severe hip OA.[74 75]

Study III

A recent study comparing self-reported outcomes across international THA registries reported a pooled mean OHS preoperative score of 20 points.[80] This is lower than the mean OHS baseline scores displayed both in the PROHIP and Non-PROHIP groups in the current study. In this context, this indicates less self-reported pain and impairments in function in participants in both groups in comparison to a more general population of individuals with severe hip OA before THA surgery. On the other hand, it could represent national variation, since the reported preoperative mean OHS range between 18 and 23 points across individual registries.[80] This observed variation may possibly be due to ethnic and cultural differences between countries, indication for THA and access to surgery, and healthcare systems.[80]

Among participants enrolled in the PROHIP group, the mean baseline scores on each of the five HOOS subscale scores were comparable to the baseline scores of individuals with severe hip OA scheduled for THA enrolled in a previous randomised controlled trial that investigated both the preoperative and postoperative efficacy of PRT performed prior to THA surgery in comparison to usual preoperative care.[75 192] The current results indicated possibly clinical significant better baseline

scores in the HOOS function in activities of daily living, function in sports and recreation, and hip-related quality of life subscales between the two groups in favour of the PROHIP group. This may suggest that individuals with severe hip OA who accept enrolment in randomised controlled trials with PRT interventions have less hip pain and impaired function than those who decline, possibly limiting generalisability to clinical practice.

Although a qualitative patient and public involvement study was conducted to inform the development of the trial protocol to improve the study design, patient information and materials, enrolment procedures, and selection of outcomes the enrolment rate of all individuals assessed for eligibility was 7.4% in PROHIP. This is comparable with the enrolment rate of 6.8% from a previous randomised controlled trial that compared TKA with non-surgical treatment among individuals with moderate to severe knee OA, which reported no use of a patient and public involvement strategy.[95] This indicate that the current patient and public involvement strategy had a minimal to almost no impact on the enrolment rate of the randomised controlled trial, which is in contrast to findings from previous a meta-analysis.[105] On the other hand, the marginal impact of the current patient and public involvement strategy could also be due to that enrolment occurred during the COVID-19 pandemic. In support of this notion, previous findings indicate that individuals with cancer appeared less likely to consider enrolment in randomised controlled trials even after hospitals returned to their pre-pandemic state during this period.[194] Overall, the current low enrolment rate in PROHIP underlines the highly demanding challenge of recruiting individuals for randomised controlled trials comparing surgical procedures with non-surgical treatment, as reported in previous trials.[95 96 98 99 195 196]

Exercise is recommended as a part of the core treatment in the management of hip OA,[45 52-57] and findings from a previous meta-analysis indicated that around 40% of individuals with hip OA are recommended or referred to exercise in clinical practice.[180] This is higher than the frequency of participants in PROHIP who previously had attended supervised exercise, but similar to the frequency of participants in Non-PROHIP. This may suggest decreased experience with previous non-surgical

treatment among individuals with severe hip OA enrolled in the randomised controlled trial.

Study IV

This is the first randomised controlled trial that have assessed the direct head-to-head effectiveness between THA and PRT among individuals with severe hip OA considered eligible for surgery. In support, two recent studies including an umbrella review of meta-analyses and a systematic review with meta-analysis investigated the effectiveness of common surgical procedures for a wide range of musculoskeletal conditions, and they found no randomised controlled trials that compared THA with non-surgical treatment.[92 93] Both studies indicated with a low certainty of evidence lack of superiority for most surgical procedures.[92 93] On the other hand, a previous randomised controlled trial showed that TKA followed by non-surgical treatment (i.e., neuromuscular exercise, patient education, dietary advice, use of insoles, and analgesics) led to clinically important greater improvements in self-reported pain, physical function and quality of life after 12 months compared with non-surgical treatment alone among individuals with moderate to severe knee OA,[95] in line with the current findings. However, the findings from the current trial demonstrated greater differences between the two groups in mean improvement in all individual outcome domains of self-reported pain, physical function and quality of life in favour of THA, as compared with the previous trial on TKA. This may be explained by that THA provided larger improvements, while PRT to some extent offered smaller improvements in the current trial than those found from TKA and non-surgical treatment in the previous trial, respectively. This seem to indicate that surgical treatment is more effective, whereas non-surgical treatment is slightly less effective in improving self-reported outcomes in individuals with hip severe OA in comparison to individuals with moderate to severe knee, as suggested in previous studies.[3 39 65 80 197]

Despite the current findings favoured THA for almost all of self-reported outcomes there were no additional clinically important improvements in gait function and no differences in sit-to-stand, as compared with PRT. Since previous studies have found large improvements

in self-reported pain, physical function, and quality of life, and only minor improvements in functional performance after THA in individuals with hip OA,[198 199] the current finding may suggest that THA is most likely no better than PRT in improving performance-based gait and sit-to-stand function. Additionally, 1 out of 3 in the PRT group experienced clinically relevant improvements in self-reported hip pain and function. These findings seem to suggest that PRT may be considered as a treatment option for a selected subgroup of individuals in the management of severe hip OA, in line with findings from a previous randomised controlled trial comparing PRT with usual preoperative care prior to THA.[75] Even for individuals with severe hip OA progressing to THA, participation in supervised PRT prior to surgery appear to be associated with some clinical benefits that indicate faster postoperative recovery.[192 200]

In general, the current findings provides evidence supporting current guideline recommendations for the referral to THA, which should only be considered for individuals with symptoms that substantially impacts quality of life and where non-surgical treatment is either ineffective or deemed inappropriate.[45] The benefits and harms of THA and PRT highlights the importance of actively engaging individuals with hip OA and considering values and preferences in shared decision-making in order to support and develop an individual tailored treatment plan.

Limitations and strengths

Study I

This qualitative study has several limitations and strengths. A main limitation is that only one focus group interview was performed for each of the groups with clinician and decision maker stakeholders due to time limitations. This may have impacted the likelihood of attaining data saturation, and thus important perceptions may have been missed in these two key stakeholder groups. Another limitation is that 3 out of 14 patient stakeholders had previously undergone THA surgery, which possibly could have influenced their views and perceptions, as previous surgery has been proposed to influence treatment expectations.[178] In addition, all patient

stakeholders were also scheduled for THA surgery, which may have affected them largely to be in favour of surgical treatment.

Strengths of this qualitative study are the wide variation in the sample of patient stakeholders, including females and males of different ages and varying levels of self-reported hip pain and functional disability recruited from both a regional hospital and a university hospital. Furthermore, three key stakeholder groups involved in receiving and delivering treatment as well as making decisions about the management of hip OA were interviewed in order to obtain several perspectives and extend the scope of the findings. Finally, an independent qualitative researcher not otherwise involved in the development or conduct of the randomised controlled trial performed the data analysis. This was done to increase neutrality in the interpretation of data and generation of the thematic network due to clinical interests of conflict amongst members of the PROHIP trial steering committee.

Study II

As this was the trial protocol, the limitations and strengths were identical with the randomised controlled trial. See Study IV down below for the detailed description.

Study III

This cross-sectional study has a number of limitations and strengths. A substantial limitation is the low enrolment rate in Non-PROHIP, in which only 293 (43.0%) out of 681 eligible individuals accepted enrolment (Figure 19). This may possibly have reduced the representativeness of the participants in Non-PROHIP, thereby affecting the current interpretation of the generalisability of the randomised controlled trial. Another limitation is that no formal a priori sample size and power calculation was conducted. This may have increased the risk of type I and type II errors in the current estimates and also limited the ability of making generalisations of the results. However, a post hoc power calculation based on the current baseline OHS scores and SD in the PROHIP and Non-PROHIP groups, with total sample size of 402 participants and group ratio of 2.7 yielded 92%

power in the primary outcome variable. A further limitation is that only self-reported characteristics and outcome scores were attained from participants in the Non-PROHIP group. Therefore, it is unknown whether clinically important group differences are present in performance-based function tests, such as those recommended by OARSI.[146] However, all of the self-reported outcome measures covers essential domains such as hip pain, physical function and quality of life in line with current guidelines for the design and conduct of randomised controlled trials involving participants with hip OA.[189-191] A minor limitation is the slightly different data collection procedures used to obtain self-reported baseline characteristics and outcome scores in the two groups. Participants in the PROHIP group completed the electronic questionnaires in an undisturbed room at one the four hospitals with the opportunity of asking clarifying questions, while participants in the non-PROHIP group completed them at home without the possibility of asking clarifying questions. This marginal difference in data collection procedures may have introduced a small risk of detection bias, possibly influencing the current baseline results.

The strengths of this cross-sectional study include the multicentre cross-sectional design with enrolment from four hospitals with orthopaedic department outpatient clinics highly specialised in hip surgery covering 3 out of 5 healthcare regions in Denmark. The analyses of self-reported characteristics and outcomes followed a predefined statistical analysis plan made publicly available at ClinicalTrials.gov before any of the analyses commenced. Lastly, balance diagnostics were used for comparing the distribution of baseline variables between the two groups in addition to statistical hypothesis testing, as this approach is not affected by sample size.[172]

Study IV

This randomised controlled trial has some limitations and strengths. A major limitation is the low enrolment rate of 7.4% with higher OHS scores at baseline, indicating less hip pain and function among participants in the trial compared with participants from an observational cohort (Study III), and a general population of individuals with hip OA from international THA

registries undergoing surgery.[80] This may suggest that the current findings should be generalised with caution. Another limitation of the current trial design is that it did not include treatment groups receiving sham surgery or exercise. Therefore, the current results may overestimate the effects attributed to both treatments, as surgical procedures and, to a lesser extent; exercise interventions are associated with contextual non-specific placebo effects.[201-204] An additional limitation is that 5 (9.4%) participants in the THA group did not undergo surgery and 12 (21.4%) participants in the PRT group received THA surgery during the 6 months follow-up. This may underestimate or overestimate the true difference between THA and PRT, although the sensitivity analyses indicated robust estimates. A further limitation is that there was one deviation from the trial protocol, as SAEs were not retrieved from the Danish National Patient Registry as originally planned. This was due to substantially delayed processing times for applications during and after the COVID-19 pandemic, which may have underestimated harms related to the THA and PRT treatments in this trial. However, SAEs were still retrieved from participant self-report and by reviewing hospital records, and thus it is unlikely to have noticeably impacted the current results. A final minor limitation is that there were differences in discharge criteria and postoperative procedures after THA surgery between the four hospitals (Table 3; Appendix 1), hypothetically affecting the effects attributed to THA surgery. However, this is considered improbable to have influenced the current results, since there are no apparent differences in effectiveness between non-supervised home-based and supervised postoperative rehabilitation after THA surgery.[54 89 205]

The strengths of this trial are the multicentre, assessor blinded (i.e., functional performance outcomes), randomised controlled design with a priori trial registration at ClinicalTrials.gov. Further strengths included a comprehensive patient and public involvement strategy used in the development of the trial protocol, publication of a pre-specified trial protocol, public available statistical analysis plan uploaded before the enrolment deadline was reached, as well as blinded interpretation of the intention-to-treat analysis. These steps ensured methodological rigorousness and basis for a high-quality trial.

Conclusion

This qualitative patient and public involvement study suggested that patient, clinician, and decision maker stakeholders had treatment expectations and beliefs that could potentially impact enrolment procedures resulting in selection bias and decreased generalisability of the randomised controlled trial. Furthermore, several facilitators and barriers were identified for THA surgery and PRT, and these could possibly affect retention rates and treatment crossovers during the follow-up period in the trial. To improve methodological rigorousness of the trial protocol, several strategies and considerations were implemented. In this regard, a parallel prospective observational cohort was included in order to assess the influence of a potential low enrolment rate. An enrolment procedure was developed that used standardised generic guidance, in which an independent clinician group was selected to deliver detailed verbal information to facilitate communication of clinical equipoise. Change in self-reported hip pain and function was selected as the primary outcome. These findings highlight the importance of using patient and public involvement in the development of a protocols for randomised controlled trials comparing surgical and surgical treatment to reduce the risk of bias.

A protocol for a high-quality randomised controlled trial comparing THA with PRT was designed, described, initiated, and completed with enrolment of 109 participants.

This cross-sectional study indicated that individuals with hip OA considered eligible for THA who were enrolled in the randomised controlled trial had different self-reported baseline characteristics and outcome scores than those who were enrolled in the parallel observational cohort. Specifically, enrolment in the trial appeared associated with less hip pain and impairments in function, higher body mass index, and lower likelihood of having previously received total joint arthroplasty surgery or non-surgical treatment. Better scores on the OHS, HOOS subscales, EQ-5D index score, and EQ-VAS and higher body mass index at baseline were associated with increased odds of accepting enrolment in the randomised

controlled trial, while worse baseline scores on the VAS and previous THA, TKA and supervised exercise were associated with reduced odds. These findings highlight to which individuals with hip OA the results from the randomised controlled trial may apply for in clinical practice.

This multicentre, randomised controlled trial demonstrated that THA were clinically significant more effective than PRT in improving in self-reported hip pain and function at 6 months follow-up. Around 3 out of 4 assigned to receive THA surgery experienced clinically important improvements hip pain and function compared with 1 out of 3 assigned to receive PRT. These findings support current recommendations for the referral to THA surgery in the management of hip OA in clinical practice.

Perspectives and Implications

Implications for clinical practice

The findings indicated robust evidence supporting superiority of THA over PRT in improving self-reported hip pain and function. Clinicians in the primary and secondary healthcare sectors may recommend THA as a more effective treatment for individuals with hip OA who have failed to respond satisfactorily to supervised exercise and patient education interventions. In this regard, clinicians should engage individuals with hip OA in shared decision-making, providing them with comprehensive information about the head-to-head benefits and risks between the surgical and non-surgical treatment approaches. This may assist individuals with hip OA in making well-informed decisions about choosing a treatment strategy based both on up to date evidence from clinical research and on the individuals specific goals, preferences, and expectations.

Implications for research

Future studies comparing surgical procedures with non-surgical treatments should consider using patient and public involvement in the development of trial protocol, as it may offer wide a range of advantages. These appear to include optimisation of enrolment and retention procedures to reduce the risk of bias as well as improving selection of important outcomes. Patient and public involvement also contribute to ensure that the research questions are meaningful to those stakeholders who may benefit from the findings.

Further investigations are required to evaluate the long-term (e.g., 1 year, 2 years and 5 years) comparative effectiveness between THA and PRT. In particular, this may provide valuable insights into whether the treatment effect are sustained in those who experienced clinically relevant improvements from receiving PRT, or whether they end up having THA surgery at one point in time.

Additional research is needed to explore whether certain subgroups of individuals with hip OA benefit more from either THA or PRT,

as factors such as sex, age, symptom severity, and previous surgery possibly may affect treatment outcomes. These subgroups analyses enable important detailed information that may be used to guide treatment selection and improve personalised healthcare for individuals with hip OA.

Further research is also necessary to evaluate the cost-effectiveness of THA compared with PRT. An assessment of the economic burden of both treatments, including the direct healthcare costs, non-healthcare-related costs, and self-reported outcomes may be used to inform healthcare decision-making.

References

1. Brandt KD, Radin EL, Dieppe PA, et al. Yet more evidence that osteoarthritis is not a cartilage disease. *Ann Rheum Dis* 2006;65(10):1261-4. doi: 10.1136/ard.2006.058347 [published Online First: 2006/09/16]
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *The Lancet* 2019;393(10182):1745-59. doi: 10.1016/s0140-6736(19)30417-9
3. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* 2021;325(6):568-78. doi: 10.1001/jama.2020.22171 [published Online First: 2021/02/10]
4. Kraus VB, Blanco FJ, Englund M, et al. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage* 2015;23(8):1233-41. doi: 10.1016/j.joca.2015.03.036 [published Online First: 2015/04/14]
5. Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79(6):819-28. doi: 10.1136/annrheumdis-2019-216515 [published Online First: 2020/05/14]
6. G.B.D. 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9 [published Online First: 2020/10/19]
7. Long H, Liu Q, Yin H, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. *Arthritis Rheumatol* 2022;74(7):1172-83. doi: 10.1002/art.42089 [published Online First: 2022/03/03]
8. Puig-Junoy J, Ruiz Zamora A. Socio-economic costs of osteoarthritis: a systematic review of cost-of-illness studies. *Semin Arthritis Rheum* 2015;44(5):531-41. doi: 10.1016/j.semarthrit.2014.10.012 [published Online First: 2014/12/17]
9. Turkiewicz A, Petersson IF, Björk J, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. *Osteoarthritis Cartilage* 2014;22(11):1826-32. doi: 10.1016/j.joca.2014.07.015 [published Online First: 2014/08/02]

10. Pereira D, Peleteiro B, Araujo J, et al. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage* 2011;19(11):1270-85. doi: 10.1016/j.joca.2011.08.009 [published Online First: 2011/09/13]
11. Kim C, Linsenmeyer KD, Vlad SC, et al. Prevalence of Radiographic and Symptomatic Hip Osteoarthritis in an Urban United States Community: The Framingham Osteoarthritis Study. *Arthritis & Rheumatology* 2014;66(11):3013-17. doi: 10.1002/art.38795
12. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *J Rheumatol* 2009;36(4):809-15. doi: 10.3899/jrheum.080677 [published Online First: 2009/03/17]
13. Murphy NJ, Eyles JP, Hunter DJ. Hip Osteoarthritis: Etiopathogenesis and Implications for Management. *Adv Ther* 2016;33(11):1921-46. doi: 10.1007/s12325-016-0409-3 [published Online First: 2016/10/28]
14. Fu M, Zhou H, Li Y, et al. Global, regional, and national burdens of hip osteoarthritis from 1990 to 2019: estimates from the 2019 Global Burden of Disease Study. *Arthritis Res Ther* 2022;24(1):8. doi: 10.1186/s13075-021-02705-6 [published Online First: 2022/01/05]
15. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet* 2015;386(9991):376-87. doi: 10.1016/s0140-6736(14)60802-3 [published Online First: 2015/03/10]
16. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med* 2010;26(3):355-69. doi: 10.1016/j.cger.2010.03.001 [published Online First: 2010/08/12]
17. Palazzo C, Nguyen C, Lefevre-Colau MM, et al. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med* 2016;59(3):134-38. doi: 10.1016/j.rehab.2016.01.006 [published Online First: 2016/02/26]
18. Saberi Hosnijeh F, Kavousi M, Boer CG, et al. Development of a prediction model for future risk of radiographic hip osteoarthritis. *Osteoarthritis Cartilage* 2018;26(4):540-46. doi: 10.1016/j.joca.2018.01.015 [published Online First: 2018/02/01]
19. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13(9):769-81. doi: 10.1016/j.joca.2005.04.014 [published Online First: 2005/06/28]
20. Cooper C, Inskip H, Croft P, et al. Individual risk factors for hip osteoarthritis: obesity, hip injury, and physical activity. *Am J*

Epidemiol 1998;147(6):516-22. doi: 10.1093/oxfordjournals.aje.a009482 [published Online First: 1998/04/01]

21. Ackerman IN, Osborne RH. Obesity and increased burden of hip and knee joint disease in Australia: results from a national survey. *BMC Musculoskelet Disord* 2012;13:254. doi: 10.1186/1471-2474-13-254 [published Online First: 2012/12/21]
22. Grotle M, Hagen KB, Natvig B, et al. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord* 2008;9:132. doi: 10.1186/1471-2474-9-132 [published Online First: 2008/10/04]
23. Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study. *J Epidemiol Community Health* 2012;66(8):678-83. doi: 10.1136/jech-2011-200834 [published Online First: 2012/04/19]
24. Lievense AM, Bierma-Zeinstra SM, Verhagen AP, et al. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. *Rheumatology (Oxford)* 2002;41(10):1155-62. doi: 10.1093/rheumatology/41.10.1155 [published Online First: 2002/10/05]
25. Richmond SA, Fukuchi RK, Ezzat A, et al. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. *J Orthop Sports Phys Ther* 2013;43(8):515-b19. doi: 10.2519/jospt.2013.4796 [published Online First: 2013/06/13]
26. Jiang L, Rong J, Wang Y, et al. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 2011;78(2):150-5. doi: 10.1016/j.jbspin.2010.04.011 [published Online First: 2010/06/29]
27. Sandell LJ. Etiology of osteoarthritis: genetics and synovial joint development. *Nat Rev Rheumatol* 2012;8(2):77-89. doi: 10.1038/nrrheum.2011.199 [published Online First: 2012/01/11]
28. Schram B, Orr R, Pope R, et al. Risk factors for development of lower limb osteoarthritis in physically demanding occupations: A narrative umbrella review. *J Occup Health* 2020;62(1):e12103. doi: 10.1002/1348-9585.12103 [published Online First: 2019/12/13]

29. Juhakoski R, Heliovaara M, Impivaara O, et al. Risk factors for the development of hip osteoarthritis: a population-based prospective study. *Rheumatology (Oxford)* 2009;48(1):83-7. doi: 10.1093/rheumatology/ken427 [published Online First: 2008/12/06]
30. Vigdorchik JM, Nepple JJ, Eftekhary N, et al. What Is the Association of Elite Sporting Activities With the Development of Hip Osteoarthritis? *Am J Sports Med* 2017;45(4):961-64. doi: 10.1177/0363546516656359 [published Online First: 2016/07/31]
31. Ganz R, Parvizi J, Beck M, et al. Femoroacetabular impingement: a cause for osteoarthritis of the hip. *Clin Orthop Relat Res* 2003(417):112-20. doi: 10.1097/01.blo.0000096804.78689.c2 [published Online First: 2003/12/04]
32. Burgess LC, Taylor P, Wainwright TW, et al. Strength and endurance deficits in adults with moderate-to-severe hip osteoarthritis, compared to healthy, older adults. *Disabil Rehabil* 2022;44(19):5563-70. doi: 10.1080/09638288.2021.1939797 [published Online First: 2021/06/23]
33. Judd DL, Thomas AC, Dayton MR, et al. Strength and functional deficits in individuals with hip osteoarthritis compared to healthy, older adults. *Disabil Rehabil* 2014;36(4):307-12. doi: 10.3109/09638288.2013.790491 [published Online First: 2013/05/11]
34. Loureiro A, Constantinou M, Diamond LE, et al. Individuals with mild-to-moderate hip osteoarthritis have lower limb muscle strength and volume deficits. *BMC Musculoskelet Disord* 2018;19(1):303. doi: 10.1186/s12891-018-2230-4 [published Online First: 2018/08/23]
35. Loureiro A, Mills PM, Barrett RS. Muscle weakness in hip osteoarthritis: a systematic review. *Arthritis Care Res (Hoboken)* 2013;65(3):340-52. doi: 10.1002/acr.21806 [published Online First: 2012/07/27]
36. Zacharias A, Green RA, Semciw A, et al. Atrophy of hip abductor muscles is related to clinical severity in a hip osteoarthritis population. *Clin Anat* 2018;31(4):507-13. doi: 10.1002/ca.23064 [published Online First: 2018/02/16]
37. Zacharias A, Pizzari T, English DJ, et al. Hip abductor muscle volume in hip osteoarthritis and matched controls. *Osteoarthritis Cartilage* 2016;24(10):1727-35. doi: 10.1016/j.joca.2016.05.002 [published Online First: 2016/05/11]
38. Gelber AC, Hochberg MC, Mead LA, et al. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern*

Med 2000;133(5):321-8. doi: 10.7326/0003-4819-133-5-200009050-00007 [published Online First: 2000/09/09]

39. Hall M, van der Esch M, Hinman RS, et al. How does hip osteoarthritis differ from knee osteoarthritis? *Osteoarthritis Cartilage* 2022;30(1):32-41. doi: 10.1016/j.joca.2021.09.010 [published Online First: 2021/10/03]
40. Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016;12(7):412-20. doi: 10.1038/nrrheum.2016.65 [published Online First: 2016/05/20]
41. Hsia AW, Emami AJ, Tarke FD, et al. Osteophytes and fracture calluses share developmental milestones and are diminished by unloading. *J Orthop Res* 2018;36(2):699-710. doi: 10.1002/jor.23779 [published Online First: 2017/10/24]
42. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: the genesis of pain. *Rheumatology (Oxford)* 2018;57(suppl_4):iv43-iv50. doi: 10.1093/rheumatology/kex419 [published Online First: 2017/12/22]
43. Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008;16(4):415-22. doi: 10.1016/j.joca.2007.12.017 [published Online First: 2008/02/26]
44. Metcalfe D, Perry DC, Claireaux HA, et al. Does This Patient Have Hip Osteoarthritis?: The Rational Clinical Examination Systematic Review. *Jama* 2019;322(23):2323-33. doi: 10.1001/jama.2019.19413 [published Online First: 2019/12/18]
45. National Institute for Health and Care Excellence. Osteoarthritis in over 16s: diagnosis and management. London. , 2022.
46. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991;34(5):505-14. doi: 10.1002/art.1780340502 [published Online First: 1991/05/01]
47. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16(4):494-502. doi: 10.1136/ard.16.4.494 [published Online First: 1957/12/01]
48. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15 Suppl A:A1-56. doi: 10.1016/j.joca.2006.11.009 [published Online First: 2007/02/27]
49. Gossec L, Jordan JM, Lam MA, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for hip osteoarthritis in terms of validity and reproducibility in 1404

radiographs: report of the OARSI-OMERACT Task Force. *Osteoarthritis Cartilage* 2009;17(2):182-7. doi: 10.1016/j.joca.2008.06.009 [published Online First: 2008/08/12]

50. Kim C, Nevitt MC, Niu J, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. *BMJ* 2015;351:h5983. doi: 10.1136/bmj.h5983 [published Online First: 2015/12/04]
51. Kinds MB, Welsing PM, Vignon EP, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. *Osteoarthritis Cartilage* 2011;19(7):768-78. doi: 10.1016/j.joca.2011.01.015 [published Online First: 2011/02/02]
52. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27(11):1578-89. doi: 10.1016/j.joca.2019.06.011 [published Online First: 2019/07/07]
53. Brosseau L, Wells GA, Pugh AG, et al. Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercise in the management of hip osteoarthritis. *Clin Rehabil* 2016;30(10):935-46. doi: 10.1177/0269215515606198 [published Online First: 2015/09/25]
54. Danish Health Authority. National Clinical Guideline For Hip Osteoarthritis - Non-surgical Treatment and Rehabilitation Following Total Hip Arthroplasty. 2nd ed: Danish Health Authority, 2021.
55. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72(7):1125-35. doi: 10.1136/annrheumdis-2012-202745 [published Online First: 2013/04/19]
56. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)* 2020;72(2):149-62. doi: 10.1002/acr.24131 [published Online First: 2020/01/08]
57. van Doormaal MCM, Meerhoff GA, Vliet Vlieland TPM, et al. A clinical practice guideline for physical therapy in patients with hip or knee osteoarthritis. *Musculoskeletal Care* 2020 doi: 10.1002/msc.1492 [published Online First: 2020/07/10]
58. Fransen M, McConnell S, Hernandez-Molina G, et al. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2014(4):Cd007912. doi: 10.1002/14651858.CD007912.pub2 [published Online First: 2014/04/24]

59. Goh SL, Persson MSM, Stocks J, et al. Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: A systematic review and meta-analysis. *Ann Phys Rehabil Med* 2019;62(5):356-65. doi: 10.1016/j.rehab.2019.04.006 [published Online First: 2019/05/24]

60. Teirlinck CH, Verhagen AP, van Ravesteyn LM, et al. Effect of exercise therapy in patients with hip osteoarthritis: A systematic review and cumulative meta-analysis. *Osteoarthr Cartil Open* 2023;5(1):100338. doi: 10.1016/j.ocarto.2023.100338 [published Online First: 2023/02/24]

61. Weng Q, Goh SL, Wu J, et al. Comparative efficacy of exercise therapy and oral non-steroidal anti-inflammatory drugs and paracetamol for knee or hip osteoarthritis: a network meta-analysis of randomised controlled trials. *Br J Sports Med* 2023 doi: 10.1136/bjsports-2022-105898 [published Online First: 2023/01/03]

62. Mazzei DR, Ademola A, Abbott JH, et al. Are education, exercise and diet interventions a cost-effective treatment to manage hip and knee osteoarthritis? A systematic review. *Osteoarthritis Cartilage* 2021;29(4):456-70. doi: 10.1016/j.joca.2020.10.002 [published Online First: 2020/11/17]

63. Dell'Isola A, Jönsson T, Rolfson O, et al. Willingness to Undergo Joint Surgery Following a First-Line Intervention for Osteoarthritis: Data From the Better Management of People With Osteoarthritis Register. *Arthritis Care Res (Hoboken)* 2021;73(6):818-27. doi: 10.1002/acr.24486 [published Online First: 2020/10/15]

64. Svege I, Nordsletten L, Fernandes L, et al. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. *Ann Rheum Dis* 2015;74(1):164-9. doi: 10.1136/annrheumdis-2013-203628 [published Online First: 2013/11/21]

65. Young JJ, Pedersen JR, Bricca A. Exercise Therapy for Knee and Hip Osteoarthritis: Is There An Ideal Prescription? *Current Treatment Options in Rheumatology* 2023 doi: 10.1007/s40674-023-00205-z

66. James KA, von Heideken J, Iversen MD. Reporting of Adverse Events in Randomized Controlled Trials of Therapeutic Exercise for Hip Osteoarthritis: A Systematic Review. *Phys Ther* 2021;101(11) doi: 10.1093/ptj/pzab195 [published Online First: 2021/11/04]

67. Mechlenburg I, Reimer LCU, Kjeldsen T, et al. Exercise as Medicine During the Course of Hip Osteoarthritis. *Exerc Sport Sci Rev* 2021;49(2):77-87. doi: 10.1249/jes.0000000000000249 [published Online First: 2021/01/23]

68. Bricca A, Juhl CB, Steultjens M, et al. Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. *Br J Sports Med* 2019;53(15):940-47. doi: 10.1136/bjsports-2017-098661 [published Online First: 2018/06/24]

69. Bricca A, Struglics A, Larsson S, et al. Impact of Exercise Therapy on Molecular Biomarkers Related to Cartilage and Inflammation in Individuals at Risk of, or With Established, Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Arthritis Care Res (Hoboken)* 2019;71(11):1504-15. doi: 10.1002/acr.23786 [published Online First: 2018/10/16]

70. Bricca A, Wirth W, Juhl CB, et al. Moderate Physical Activity and Prevention of Cartilage Loss in People With Knee Osteoarthritis: Data From the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2019;71(2):218-26. doi: 10.1002/acr.23791 [published Online First: 2018/10/20]

71. Regnaux JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database Syst Rev* 2015(10):Cd010203. doi: 10.1002/14651858.CD010203.pub2 [published Online First: 2015/10/30]

72. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43(7):1334-59. doi: 10.1249/MSS.0b013e318213fefb [published Online First: 2011/06/23]

73. Moseng T, Dagfinrud H, Smedslund G, et al. The importance of dose in land-based supervised exercise for people with hip osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage* 2017;25(10):1563-76. doi: 10.1016/j.joca.2017.06.004 [published Online First: 2017/06/27]

74. Hansen S, Mikkelsen LR, Overgaard S, et al. Effectiveness of supervised resistance training for patients with hip osteoarthritis - a systematic review. *Dan Med J* 2020;67(6) [published Online First: 2020/08/04]

75. Hermann A, Holsgaard-Larsen A, Zerahn B, et al. Preoperative progressive explosive-type resistance training is feasible and effective in patients with hip osteoarthritis scheduled for total hip arthroplasty--a randomized controlled trial. *Osteoarthritis*

Cartilage 2016;24(1):91-8. doi: 10.1016/j.joca.2015.07.030 [published Online First: 2015/08/19]

76. Wiles P. The surgery of the osteoarthritic hip. *Br J Surg* 1958;45(193):488-97. doi: 10.1002/bjs.18004519315 [published Online First: 1958/03/18]
77. Charnley J. Arthroplasty of the hip. A new operation. *Lancet* 1961;1(7187):1129-32. doi: 10.1016/s0140-6736(61)92063-3 [published Online First: 1961/05/27]
78. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet* 2007;370(9597):1508-19. doi: 10.1016/s0140-6736(07)60457-7 [published Online First: 2007/10/30]
79. Costa ML, Achten J, Parsons NR, et al. Total hip arthroplasty versus resurfacing arthroplasty in the treatment of patients with arthritis of the hip joint: single centre, parallel group, assessor blinded, randomised controlled trial. *Bmj* 2012;344:e2147. doi: 10.1136/bmj.e2147 [published Online First: 2012/04/21]
80. Ingelsrud LH, Wilkinson JM, Overgaard S, et al. How do Patient-reported Outcome Scores in International Hip and Knee Arthroplasty Registries Compare? *Clin Orthop Relat Res* 2022;480(10):1884-96. doi: 10.1097/corr.0000000000002306 [published Online First: 2022/07/29]
81. Rosenlund S, Broeng L, Holsgaard-Larsen A, et al. Patient-reported outcome after total hip arthroplasty: comparison between lateral and posterior approach. *Acta Orthop* 2017;88(3):239-47. doi: 10.1080/17453674.2017.1291100 [published Online First: 2017/05/04]
82. Shan L, Shan B, Graham D, et al. Total hip replacement: a systematic review and meta-analysis on mid-term quality of life. *Osteoarthritis Cartilage* 2014;22(3):389-406. doi: 10.1016/j.joca.2013.12.006 [published Online First: 2014/01/07]
83. Yan L, Ge L, Dong S, et al. Evaluation of Comparative Efficacy and Safety of Surgical Approaches for Total Hip Arthroplasty: A Systematic Review and Network Meta-analysis. *JAMA Netw Open* 2023;6(1):e2253942. doi: 10.1001/jamanetworkopen.2022.53942 [published Online First: 2023/02/01]
84. Danish Hip Arthroplasty Register. National Annual Report 2021. 2022. Available from: http://danskhoftealloplastikregister.dk/wp-content/uploads/2022/07/DHR-aarsrapport-2021_Udgivet-2022_offentliggjort-version.pdf.

85. National Joint Registry. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man: 19th Annual Report 2022, 2022.
86. Ferguson RJ, Palmer AJ, Taylor A, et al. Hip replacement. *Lancet* 2018;392(10158):1662-71. doi: 10.1016/s0140-6736(18)31777-x [published Online First: 2018/11/30]
87. Gademan MG, Hofstede SN, Vliet Vlieland TP, et al. Indication criteria for total hip or knee arthroplasty in osteoarthritis: a state-of-the-science overview. *BMC Musculoskelet Disord* 2016;17(1):463. doi: 10.1186/s12891-016-1325-z [published Online First: 2016/11/11]
88. Lutzner C, Deckert S, Gunther KP, et al. Indication Criteria for Total Hip Arthroplasty in Patients with Hip Osteoarthritis-Recommendations from a German Consensus Initiative. *Medicina (Kaunas)* 2022;58(5) doi: 10.3390/medicina58050574 [published Online First: 2022/05/29]
89. National Institute for Health and Care Excellence. Joint replacement (primary): hip, knee and shoulder, 2020.
90. Hermansen LL, Viberg B, Hansen L, et al. "True" Cumulative Incidence of and Risk Factors for Hip Dislocation within 2 Years After Primary Total Hip Arthroplasty Due to Osteoarthritis: A Nationwide Population-Based Study from the Danish Hip Arthroplasty Register. *J Bone Joint Surg Am* 2020;Publish Ahead of Print doi: 10.2106/jbjs.19.01352 [published Online First: 2020/12/22]
91. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;2(1):e000435. doi: 10.1136/bmjopen-2011-000435 [published Online First: 2012/02/24]
92. Blom AW, Donovan RL, Beswick AD, et al. Common elective orthopaedic procedures and their clinical effectiveness: umbrella review of level 1 evidence. *Bmj* 2021;374:n1511. doi: 10.1136/bmj.n1511 [published Online First: 2021/07/09]
93. Skou ST, Poulsen E, Bricca A, et al. Benefits and Harms of Interventions With Surgery Compared to Interventions Without Surgery for Musculoskeletal Conditions: A Systematic Review With Meta-analysis. *J Orthop Sports Phys Ther* 2022;52(6):312-44. doi: 10.2519/jospt.2022.11075 [published Online First: 2022/06/02]
94. Skou ST, Roos EM, Laursen MB, et al. Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from

two parallel randomized controlled trials. *Osteoarthritis Cartilage* 2018;26(9):1170-80. doi: 10.1016/j.joca.2018.04.014 [published Online First: 2018/05/04]

95. Skou ST, Roos EM, Laursen MB, et al. A Randomized, Controlled Trial of Total Knee Replacement. *N Engl J Med* 2015;373(17):1597-606. doi: 10.1056/NEJMoa1505467

96. Frobell RB, Roos EM, Roos HP, et al. A Randomized Trial of Treatment for Acute Anterior Cruciate Ligament Tears. *N Engl J Med* 2010;363:331-42.

97. Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med* 2013;368(18):1675-84. doi: 10.1056/NEJMoa1301408 [published Online First: 2013/03/20]

98. Skou ST, Hölmich P, Lind M, et al. Early Surgery or Exercise and Education for Meniscal Tears in Young Adults. *NEJM Evidence* 2022;1(2) doi: 10.1056/EVIDoa2100038

99. van de Graaf VA, Noorduyn JCA, Willigenburg NW, et al. Effect of Early Surgery vs Physical Therapy on Knee Function Among Patients With Nonobstructive Meniscal Tears: The ESCAPE Randomized Clinical Trial. *Jama* 2018;320(13):1328-37. doi: 10.1001/jama.2018.13308 [published Online First: 2018/10/05]

100. Kennedy-Martin T, Curtis S, Faries D, et al. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 2015;16:495. doi: 10.1186/s13063-015-1023-4 [published Online First: 2015/11/05]

101. van Deudekom FJ, Postmus I, van der Ham DJ, et al. External validity of randomized controlled trials in older adults, a systematic review. *PLoS One* 2017;12(3):e0174053. doi: 10.1371/journal.pone.0174053 [published Online First: 2017/03/28]

102. Ross S, Grant A, Counsell C, et al. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;52(12):1143-56. doi: 10.1016/s0895-4356(99)00141-9 [published Online First: 1999/12/02]

103. Coupe N, Mathieson A. Patient and public involvement in doctoral research: Impact, resources and recommendations. *Health Expect* 2020;23(1):125-36. doi: 10.1111/hex.12976 [published Online First: 2019/10/16]

104. Crocker JC, Pratt-Boyden K, Hislop J, et al. Patient and public involvement (PPI) in UK surgical trials: a survey and focus groups with stakeholders to identify practices, views, and experiences.

Trials 2019;20(1):119. doi: 10.1186/s13063-019-3183-0 [published Online First: 2019/02/13]

105. Crocker JC, Ricci-Cabello I, Parker A, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. *Bmj* 2018;363:k4738. doi: 10.1136/bmj.k4738 [published Online First: 2018/11/30]
106. Owyang D, Bakhsh A, Brewer D, et al. Patient and Public Involvement Within Orthopaedic Research: A Systematic Review. *J Bone Joint Surg Am* 2021;103(13):e51. doi: 10.2106/jbjs.20.01573 [published Online First: 2021/07/07]
107. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053 [published Online First: 2013/10/22]
108. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19(6):349-57. doi: 10.1093/intqhc/mzm042 [published Online First: 2007/09/18]
109. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
110. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007;147(8):W163-94. [published Online First: 2007/10/17]
111. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012;10(1):28-55. doi: 10.1016/j.ijsu.2011.10.001 [published Online First: 2011/11/01]
112. Slade SC, Dionne CE, Underwood M, et al. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med* 2016;50(23):1428-37. doi: 10.1136/bjsports-2016-096651 [published Online First: 2016/10/07]
113. Toigo M, Boutellier U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur J Appl Physiol* 2006;97(6):643-63. doi: 10.1007/s00421-006-0238-1 [published Online First: 2006/07/18]

114. Adom D, Yeboah A, Ankrah A. Constructivism philosophical paradigm: implication for research, teaching and learning. *GJAHSS* 2016;4:1-9.

115. Shimmin C. Methods of patient and public engagement: A guide: George and Faye Yee- Center of Healthcare Innovation; 2020 [Available from: https://static1.squarespace.com/static/5e57d5337fe0d104c77cca10/t/5ed808e613338b69dcb8f6df/1591216360358/20.05.20+PE+methods+of+Engagement+web.pdf accessed 24 July 2020.

116. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010 [published Online First: 2008/10/22]

117. Husted H. Fast-track hip and knee arthroplasty: clinical and organizational aspects. *Acta Orthop Suppl* 2012;83(346):1-39. doi: 10.3109/17453674.2012.700593 [published Online First: 2012/12/12]

118. Hoppenfeld S, de Boer P, Buckley R. The Hip. Surgical Exposures in Orthopaedics the Anatomic Approach. 4th edition ed. Philadelphia: Lippincott Williams & Wilkins 2009:403–62.

119. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2(2):92-8. [published Online First: 1970/01/01]

120. Borg G. Borg's Perceived exertion and pain scales. Champaign, IL: Human Kinetics 1998.

121. Ratamess NA, Alvar BA, Evetoch TK, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41(3):687-708. doi: 10.1249/MSS.0b013e3181915670 [published Online First: 2009/02/11]

122. Marsh AP, Miller ME, Rejeski WJ, et al. Lower extremity muscle function after strength or power training in older adults. *J Aging Phys Act* 2009;17(4):416-43. [published Online First: 2009/11/27]

123. Thomee R. A comprehensive treatment approach for patellofemoral pain syndrome in young women. *Phys Ther* 1997;77(12):1690-703. [published Online First: 1997/12/31]

124. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS),

Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S240-52. doi: 10.1002/acr.20543 [published Online First: 2012/05/25]

125. Sandal LF, Roos EM, Bogesvang SJ, et al. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. *Osteoarthritis Cartilage* 2016;24(4):589-92. doi: 10.1016/j.joca.2015.11.002 [published Online First: 2015/11/14]
126. Dawson J, Fitzpatrick R, Carr A, et al. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg Br* 1996;78(2):185-90. [published Online First: 1996/03/01]
127. Murray DW, Fitzpatrick R, Rogers K, et al. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br* 2007;89(8):1010-4. doi: 10.1302/0301-620x.89b8.19424 [published Online First: 2007/09/06]
128. Harris KK, Price AJ, Beard DJ, et al. Can pain and function be distinguished in the Oxford Hip Score in a meaningful way? : an exploratory and confirmatory factor analysis. *Bone Joint Res* 2014;3(11):305-9. doi: 10.1302/2046-3758.311.2000313 [published Online First: 2014/11/05]
129. Beard DJ, Harris K, Dawson J, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol* 2015;68(1):73-9. doi: 10.1016/j.jclinepi.2014.08.009 [published Online First: 2014/12/03]
130. Gosens T, Hoefnagels NH, de Vet RC, et al. The "Oxford Heup Score": the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. *Acta Orthop* 2005;76(2):204-11. [published Online First: 2005/08/16]
131. Harris K, Dawson J, Gibbons E, et al. Systematic review of measurement properties of patient-reported outcome measures used in patients undergoing hip and knee arthroplasty. *Patient Relat Outcome Meas* 2016;7:101-8. doi: 10.2147/prom.S97774 [published Online First: 2016/08/16]
132. Martin-Fernandez J, Gray-Laymon P, Molina-Siguero A, et al. Cross-cultural adaptation and validation of the Spanish version of the Oxford Hip Score in patients with hip osteoarthritis. *BMC Musculoskelet Disord* 2017;18(1):205. doi: 10.1186/s12891-017-1568-3 [published Online First: 2017/05/24]
133. Martinelli N, Longo UG, Marinozzi A, et al. Cross-cultural adaptation and validation with reliability, validity, and responsiveness of the Italian version of the Oxford Hip Score in patients with hip

osteoarthritis. *Qual Life Res* 2011;20(6):923-9. doi: 10.1007/s11136-010-9811-5 [published Online First: 2010/12/08]

134. Naal FD, Sieverding M, Impellizzeri FM, et al. Reliability and validity of the cross-culturally adapted German Oxford hip score. *Clin Orthop Relat Res* 2009;467(4):952-7. doi: 10.1007/s11999-008-0457-3 [published Online First: 2008/08/30]
135. Paulsen A, Odgaard A, Overgaard S. Translation, cross-cultural adaptation and validation of the Danish version of the Oxford hip score: Assessed against generic and disease-specific questionnaires. *Bone Joint Res* 2012;1(9):225-33. doi: 10.1302/2046-3758.19.2000076 [published Online First: 2013/04/24]
136. Nilsdotter AK, Lohmander LS, Klassbo M, et al. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord* 2003;4:10. doi: 10.1186/1471-2474-4-10 [published Online First: 2003/06/05]
137. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. *Scand J Rheumatol* 2003;32(1):46-51. [published Online First: 2003/03/15]
138. de Groot IB, Reijman M, Terwee CB, et al. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage* 2007;15(1):104-9. doi: 10.1016/j.joca.2006.06.014 [published Online First: 2006/08/08]
139. Thorborg K, Roos EM, Bartels EM, et al. Validity, reliability and responsiveness of patient-reported outcome questionnaires when assessing hip and groin disability: a systematic review. *Br J Sports Med* 2010;44(16):1186-96. doi: 10.1136/bjsm.2009.060889 [published Online First: 2009/08/12]
140. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64. doi: 10.1186/1477-7525-1-64 [published Online First: 2003/11/14]
141. Beyer N, Thorborg K, Vinther A. Translation and Cross-Cultural Adaptation of the Danish Version of the Hip Dysfunction and Osteoarthritis Outcome Score 2.0 (HOOS 2.0). *[http://koosnu/indexhtml]* 2008
142. Amstutz HC, Thomas BJ, Jinnah R, et al. Treatment of primary osteoarthritis of the hip. A comparison of total joint and surface replacement arthroplasty. *J Bone Joint Surg Am* 1984;66(2):228-41. [published Online First: 1984/02/01]

143. Mørup-Petersen A, Skou ST, Holm CE, et al. Measurement properties of UCLA Activity Scale for hip and knee arthroplasty patients and translation and cultural adaptation into Danish. *Acta Orthop* 2021;92(6):681-88. doi: 10.1080/17453674.2021.1977533 [published Online First: 2021/09/18]

144. Naal FD, Impellizzeri FM, Leunig M. Which is the best activity rating scale for patients undergoing total joint arthroplasty? *Clin Orthop Relat Res* 2009;467(4):958-65. doi: 10.1007/s11999-008-0358-5 [published Online First: 2008/07/01]

145. Terwee CB, Bouwmeester W, van Elsland SL, et al. Instruments to assess physical activity in patients with osteoarthritis of the hip or knee: a systematic review of measurement properties. *Osteoarthritis Cartilage* 2011;19(6):620-33. doi: 10.1016/j.joca.2011.01.002 [published Online First: 2011/01/22]

146. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21(8):1042-52. doi: 10.1016/j.joca.2013.05.002 [published Online First: 2013/05/18]

147. Wright AA, Cook CE, Baxter GD, et al. A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. *J Orthop Sports Phys Ther* 2011;41(5):319-27. doi: 10.2519/jospt.2011.3515 [published Online First: 2011/02/22]

148. Dobson F, Hinman RS, Hall M, et al. Reliability and measurement error of the Osteoarthritis Research Society International (OARSI) recommended performance-based tests of physical function in people with hip and knee osteoarthritis. *Osteoarthritis Cartilage* 2017;25(11):1792-96. doi: 10.1016/j.joca.2017.06.006 [published Online First: 2017/06/26]

149. Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. *Physiother Res Int* 2008;13(3):141-52. doi: 10.1002/pri.411 [published Online First: 2008/08/13]

150. International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use: ICH harmonised tripartite guideline. Guideline for Good Clinical Practice E6 (R1). 1996 [Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf accessed June 20, 2019.

151. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;64(1):29-33. doi: 10.1136/ard.2004.022905 [published Online First: 2004/06/23]

152. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 2011/04/12]

153. Jensen CE, Sørensen SS, Gudex C, et al. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy* 2021;19(4):579-91. doi: 10.1007/s40258-021-00639-3 [published Online First: 2021/02/03]

154. Conner-Spady BL, Marshall DA, Bohm E, et al. Reliability and validity of the EQ-5D-5L compared to the EQ-5D-3L in patients with osteoarthritis referred for hip and knee replacement. *Qual Life Res* 2015;24(7):1775-84. doi: 10.1007/s11136-014-0910-6 [published Online First: 2015/01/04]

155. Conner-Spady BL, Marshall DA, Bohm E, et al. Comparing the validity and responsiveness of the EQ-5D-5L to the Oxford hip and knee scores and SF-12 in osteoarthritis patients 1 year following total joint replacement. *Qual Life Res* 2018;27(5):1311-22. doi: 10.1007/s11136-018-1808-5 [published Online First: 2018/02/10]

156. Feng YS, Kohlmann T, Janssen MF, et al. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res* 2021;30(3):647-73. doi: 10.1007/s11136-020-02688-y [published Online First: 2020/12/08]

157. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22(7):1717-27. doi: 10.1007/s11136-012-0322-4 [published Online First: 2012/11/28]

158. Guyatt GH, Norman GR, Juniper EF, et al. A critical look at transition ratings. *J Clin Epidemiol* 2002;55(9):900-8. [published Online First: 2002/10/24]

159. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10(4):407-15. [published Online First: 1989/12/01]

160. Ingelsrud LH, Granan LP, Terwee CB, et al. Proportion of Patients Reporting Acceptable Symptoms or Treatment Failure and Their

Associated KOOS Values at 6 to 24 Months After Anterior Cruciate Ligament Reconstruction: A Study From the Norwegian Knee Ligament Registry. *Am J Sports Med* 2015;43(8):1902-7. doi: 10.1177/0363546515584041 [published Online First: 2015/05/16]

161. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. *Ann Rheum Dis* 2005;64(1):34-7. doi: 10.1136/ard.2004.023028 [published Online First: 2004/05/08]
162. Thorborg K, Petersen J, Magnusson SP, et al. Clinical assessment of hip strength using a hand-held dynamometer is reliable. *Scand J Med Sci Sports* 2010;20(3):493-501. doi: 10.1111/j.1600-0838.2009.00958.x [published Online First: 2009/06/30]
163. Lipperts M, van Laarhoven S, Senden R, et al. Clinical validation of a body-fixed 3D accelerometer and algorithm for activity monitoring in orthopaedic patients. *J Orthop Translat* 2017;11:19-29. doi: 10.1016/j.jot.2017.02.003 [published Online First: 2017/02/27]
164. Sliepen M, Lipperts M, Tjur M, et al. Use of accelerometer-based activity monitoring in orthopaedics: benefits, impact and practical considerations. *EFORT Open Rev* 2019;4(12):678-85. doi: 10.1302/2058-5241.4.180041 [published Online First: 2020/02/06]
165. Lambert SD, Loiselle CG. Combining individual interviews and focus groups to enhance data richness. *J Adv Nurs* 2008;62(2):228-37. doi: 10.1111/j.1365-2648.2007.04559.x [published Online First: 2008/04/09]
166. Krueger RA, Casey MA. Designing and conducting focus group interviews: St Paul, Minnesota, USA, 2002.
167. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res* 2016;26(13):1753-60. doi: 10.1177/1049732315617444 [published Online First: 2015/11/29]
168. Judge A, Arden NK, Price A, et al. Assessing patients for joint replacement: can pre-operative Oxford hip and knee scores be used to predict patient satisfaction following joint replacement surgery and to guide patient selection? *J Bone Joint Surg Br* 2011;93(12):1660-4. doi: 10.1302/0301-620x.93b12.27046 [published Online First: 2011/12/14]

169. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. *Qualitative Research* 2001;1(3):385-405. doi: 10.1177/146879410100100307

170. Braun V, Clarke V. Thematic analysis : a practical guide. Los Angeles: SAGE 2022.

171. Polit DF, Beck CT. Nursing Research: Principles and Methods: Lippincott Williams & Wilkins 2004.

172. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28(25):3083-107. doi: 10.1002/sim.3697 [published Online First: 2009/09/17]

173. Järvinen TL, Sihvonen R, Bhandari M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol* 2014;67(7):769-72. doi: 10.1016/j.jclinepi.2013.11.011 [published Online First: 2014/02/25]

174. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *Jama* 2014;312(1):85-6. doi: 10.1001/jama.2014.7523 [published Online First: 2014/07/25]

175. Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. *Jama* 2016;315(4):407-8. doi: 10.1001/jama.2015.19394 [published Online First: 2016/01/28]

176. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. *Bmj* 2011;342:d40. doi: 10.1136/bmj.d40 [published Online First: 2011/02/09]

177. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12(5):389-99. doi: 10.1016/j.joca.2004.02.001 [published Online First: 2004/04/20]

178. Cronström A, Dahlberg LE, Nero H, et al. "I was considering surgery because I believed that was how it was treated": a qualitative study on willingness for joint surgery after completion of a digital management program for osteoarthritis. *Osteoarthritis Cartilage* 2019;27(7):1026-32. doi: 10.1016/j.joca.2019.04.004 [published Online First: 2019/04/20]

179. Nissen N, Holm PM, Bricca A, et al. Clinicians' beliefs and attitudes to physical activity and exercise therapy as treatment for knee and/or hip osteoarthritis: a scoping review. *Osteoarthritis*

Cartilage 2022;30(2):260-69. doi: 10.1016/j.joca.2021.11.008 [published Online First: 2021/11/21]

180. Hagen KB, Smedslund G, Østerås N, et al. Quality of Community-Based Osteoarthritis Care: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2016;68(10):1443-52. doi: 10.1002/acr.22891 [published Online First: 2016/03/19]
181. Beaton DE, Tarasuk V, Katz JN, et al. "Are you better?" A qualitative study of the meaning of recovery. *Arthritis Rheum* 2001;45(3):270-9. doi: 10.1002/1529-0131(200106)45:3<270::Aid-art260>3.0.Co;2-t [published Online First: 2001/06/21]
182. Myburgh C, Boyle E, Lauridsen HH, et al. What influences retrospective self-appraised recovery status among Danes with low-back problems? A comparative qualitative investigation. *J Rehabil Med* 2015;47(8):741-7. doi: 10.2340/16501977-1987 [published Online First: 2015/07/02]
183. Brembo EA, Kapstad H, Eide T, et al. Patient information and emotional needs across the hip osteoarthritis continuum: a qualitative study. *BMC Health Serv Res* 2016;16:88. doi: 10.1186/s12913-016-1342-5 [published Online First: 2016/03/13]
184. Darlow B, Dowell A, Baxter GD, et al. The enduring impact of what clinicians say to people with low back pain. *Ann Fam Med* 2013;11(6):527-34. doi: 10.1370/afm.1518 [published Online First: 2013/11/13]
185. Ackerman IN, Dieppe PA, March LM, et al. Variation in age and physical status prior to total knee and hip replacement surgery: a comparison of centers in Australia and Europe. *Arthritis Rheum* 2009;61(2):166-73. doi: 10.1002/art.24215 [published Online First: 2009/01/30]
186. Cobos R, Latorre A, Aizpuru F, et al. Variability of indication criteria in knee and hip replacement: an observational study. *BMC Musculoskelet Disord* 2010;11:249. doi: 10.1186/1471-2474-11-249 [published Online First: 2010/10/28]
187. Dreinhöfer KE, Dieppe P, Stürmer T, et al. Indications for total hip replacement: comparison of assessments of orthopaedic surgeons and referring physicians. *Ann Rheum Dis* 2006;65(10):1346-50. doi: 10.1136/ard.2005.047811 [published Online First: 2006/01/28]
188. Darlow B, Brown M, Thompson B, et al. Living with osteoarthritis is a balancing act: an exploration of patients' beliefs about knee pain.

BMC Rheumatol 2018;2:15. doi: 10.1186/s41927-018-0023-x [published Online First: 2019/03/20]

189. Lane NE, Hochberg MC, Nevitt MC, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hip osteoarthritis. *Osteoarthritis Cartilage* 2015;23(5):761-71. doi: 10.1016/j.joca.2015.03.006 [published Online First: 2015/05/09]
190. Allen KD, Huffman K, Cleveland RJ, et al. Evaluating Osteoarthritis Management Programs: outcome domain recommendations from the OARSI Joint Effort Initiative. *Osteoarthritis Cartilage* 2023 doi: 10.1016/j.joca.2023.02.078 [published Online First: 2023/03/10]
191. Smith TO, Hawker GA, Hunter DJ, et al. The OMERACT-OARSI Core Domain Set for Measurement in Clinical Trials of Hip and/or Knee Osteoarthritis. *J Rheumatol* 2019;46(8):981-89. doi: 10.3899/jrheum.181194 [published Online First: 2019/01/17]
192. Holsgaard-Larsen A, Hermann A, Zerahn B, et al. Effects of progressive resistance training prior to total HIP arthroplasty - A secondary analysis of a randomized controlled trial. *Osteoarthritis Cartilage* 2020 doi: 10.1016/j.joca.2020.04.010 [published Online First: 2020/05/08]
193. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc* 2009;41(7):1510-30. doi: 10.1249/MSS.0b013e3181a0c95c [published Online First: 2009/06/12]
194. Fleury ME, Farner AM, Unger JM. Association of the COVID-19 Outbreak With Patient Willingness to Enroll in Cancer Clinical Trials. *JAMA Oncol* 2021;7(1):131-32. doi: 10.1001/jamaoncol.2020.5748 [published Online First: 2020/11/13]
195. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *Jama* 2006;296(20):2441-50. doi: 10.1001/jama.296.20.2441 [published Online First: 2006/11/23]
196. Frobell RB, Roos EM, Roos HP, et al. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med* 2010;363(4):331-42. doi: 10.1056/NEJMoa0907797 [published Online First: 2010/07/28]
197. Bourne RB, Chesworth B, Davis A, et al. Comparing patient outcomes after THA and TKA: is there a difference? *Clin Orthop Relat Res* 2010;468(2):542-6. doi: 10.1007/s11999-009-1046-9 [published Online First: 2009/09/18]

198. Judd DL, Dennis DA, Thomas AC, et al. Muscle strength and functional recovery during the first year after THA. *Clin Orthop Relat Res* 2014;472(2):654-64. doi: 10.1007/s11999-013-3136-y [published Online First: 2013/07/03]

199. Vissers MM, Bussmann JB, Verhaar JA, et al. Recovery of physical functioning after total hip arthroplasty: systematic review and meta-analysis of the literature. *Phys Ther* 2011;91(5):615-29. doi: 10.2522/ptj.20100201 [published Online First: 2011/03/12]

200. Jørgensen SL, Kierkegaard S, Bohn MB, et al. Effects of Resistance Training Prior to Total Hip or Knee Replacement on Post-operative Recovery in Functional Performance: A Systematic Review and Meta-Analysis. *Front Sports Act Living* 2022;4:924307. doi: 10.3389/fspor.2022.924307 [published Online First: 2022/08/02]

201. Bandak E, Christensen R, Overgaard A, et al. Exercise and education versus saline injections for knee osteoarthritis: a randomised controlled equivalence trial. *Ann Rheum Dis* 2022;81(4):537-43. doi: 10.1136/annrheumdis-2021-221129 [published Online First: 2021/12/01]

202. Bennell KL, Egerton T, Martin J, et al. Effect of physical therapy on pain and function in patients with hip osteoarthritis: a randomized clinical trial. *JAMA* 2014;311(19):1987-97. doi: 10.1001/jama.2014.4591 [published Online First: 2014/05/23]

203. Messier SP, Mihalko SL, Beavers DP, et al. Effect of High-Intensity Strength Training on Knee Pain and Knee Joint Compressive Forces Among Adults With Knee Osteoarthritis: The START Randomized Clinical Trial. *JAMA* 2021;325(7):646-57. doi: 10.1001/jama.2021.0411 [published Online First: 2021/02/17]

204. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ* 2014;348:g3253. doi: 10.1136/bmj.g3253 [published Online First: 2014/05/23]

205. Hansen S, Aaboe J, Mechlenburg I, et al. Effects of supervised exercise compared to non-supervised exercise early after total hip replacement on patient-reported function, pain, health-related quality of life and performance-based function - a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil* 2019;33(1):13-23. doi: 10.1177/0269215518791213 [published Online First: 2018/08/04]

Appendices

Appendix 7. Sensitivity analyses for Study IV, p. 210

Appendix 8. Paper for Study I, p. 213

Frydendal T, Thomsen KS, Mechlenburg I, Mikkelsen LR, Overgaard S, Ingwersen KG, Myburgh C. *Patient and Public Involvement to Inform The Protocol of a Clinical Trial Comparing Total Hip Arthroplasty With Exercise: An Explorative Qualitative Case Study*. BMJ Open 2023;13(4):e070866. doi: 10.1136/bmjopen-2022-070866.

Appendix 9. Paper for Study II, p. 226

Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Overgaard S, Ingwersen KG. *Total Hip Arthroplasty versus Progressive Resistance Training in Patients with Severe Hip Osteoarthritis: Protocol for a Multicentre, Parallel-group, Randomised Controlled Superiority Trial*. BMJ Open 2021; 11: e051392. doi: 10.1136/bmjopen-2021-051392.

Appendix 10. Manuscript for Study III, p. 240

Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Varnum C, Bieder MJ, Jakobsen SS, Overgaard S, Ingwersen KG. *Different Self-reported Characteristics and Outcome Scores in a Randomized Trial Comparing Total Hip Arthroplasty with Exercise: A Cross-sectional Study of 402 Patients with Hip Osteoarthritis*. Manuscript (submitted, under review). May 2023.

Appendix 11. Manuscript for Study IV, p. 268

Frydendal T, Christensen R, Mechlenburg I, Mikkelsen LR, Varnum C, Graversen AE, Kjærsgaard-Andersen P, Revald PH, Hofbauer C, Bieder MJ, Qassim H, Munir MS, Jakobsen SS, Nielsen SM, Ingwersen KG, Overgaard S. *Total Hip Replacement or Progressive Resistance Training for Severe Hip Osteoarthritis*. Manuscript (not submitted yet). May 2023.

sdu.dk

#sdudk

SDU
Syddansk Universitet

University of Southern Denmark
Campusvej 55
DK-5230 Odense

Phone: +45 6550 1000
sdu@sdu.dk
www.sdu.dk