Early rehabilitation after fast-track total hip replacement

Effect of early, supervised, progressive resistance training and influence of movement restrictions and assistive devices on functional recovery

PhD dissertation

Lone Ramer Mikkelsen

Health
Aarhus University
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AARHUS UNIVERSITY

Orthopaedic Research Aarhus

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Preface

This PhD thesis was accomplished during my employment at the Elective Surgery Centre (former Department of Orthopaedic Surgery) at Silkeborg Regional Hospital. It was carried out in close corporation with Orthopaedic Research Aarhus (www.orthoresearch.dk) led by my main supervisor Professor Kjeld Søballe.

First of all I would like to thank all the participating patients who have investigated time and energy in participating in these studies, without them: no studies!!

I am grateful to my three academic supervisors for their belief in me and the projects. I would like to thank Professor Kjeld Søballe for his encouragement and advices, especially concerning the design of the studies, and for sharing with me his impressive knowledge within hip replacement surgery and clinical research methods. I send my gratitude to my supervisor Inger Mechlenburg, PhD, for her role as a mentor, giving me encouragement during hard times and counselling concerning scientific questions as well as the difficult balance between work and family life. I would like to praise her always constructive and very rapid response to scientific texts send to her for review. I thank my supervisor Mette Krintel Petersen, PhD, for suggesting that I should carry out this PhD in the first place, and for sharing her widespread experience on physiotherapy research and the execution of clinical intervention studies.

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My gratitude also goes to Niels Trolle Andersen for helpful statistical supervision on several occasions and senior researcher Thomas Bandholm for fruitful collaboration and several valuable advices. Furthermore, I thank my sister Ulla Ramer Mikkelsen, PhD, who has generously shared her extensive research experience within the field of sports medicine. Last, but definitely not least, I send thanks and lots of love to my husband Claus for supporting me and making this project possible by taking care of our children Freja, Malte and Selma and all the practical issues when I left on congresses and several writing stays away from home.

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Lone Ramer Mikkelsen, 2014
List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals (I-III) throughout this thesis.


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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>CG</td>
<td>Control group (Study III)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HOOS</td>
<td>Hip dysfunction and osteoarthritis outcome score questionnaire</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass correlation coefficient</td>
</tr>
<tr>
<td>IG</td>
<td>Intervention group (Study III)</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MANOVA</td>
<td>Multivariate repeated measurement analysis of variance</td>
</tr>
<tr>
<td>MDC</td>
<td>Minimal detectable change (equation: 1.96 x (\sqrt{\frac{2}{n}}) x SEM)</td>
</tr>
<tr>
<td>MDC (%)</td>
<td>MDC in per cent of the grand mean (mean of the two test sessions)</td>
</tr>
<tr>
<td>Nm</td>
<td>Newton x meter</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
</tr>
<tr>
<td>PRT</td>
<td>Progressive resistance training</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RG</td>
<td>Restricted group (Study I)</td>
</tr>
<tr>
<td>RM</td>
<td>Repetition maximum</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of measurement (equation: SD/(\sqrt{2}))</td>
</tr>
<tr>
<td>SEM (%)</td>
<td>SEM in per cent of the grand mean (mean of the two test sessions)</td>
</tr>
<tr>
<td>THR</td>
<td>Total hip replacement</td>
</tr>
<tr>
<td>TKR</td>
<td>Total knee replacement</td>
</tr>
<tr>
<td>UG</td>
<td>Unrestricted group (Study I)</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>W</td>
<td>Watt</td>
</tr>
</tbody>
</table>
1. English summary

Total hip replacement (THR) surgery results in substantial pain relief and functional gains. However, deficits in muscle strength and physical function after THR persist. Progressive resistance training (PRT) commenced early after THR can potentially reduce these deficits and thereby enhance recovery. Traditionally, rehabilitation after THR has included movement restrictions to prevent hip dislocations. Improvements in surgical techniques and increase of femoral head size may have changed the rationale for these restrictions.

The objectives of this thesis were I) to evaluate the influence of movement restrictions and assistive devices on rehabilitation after fast-track THR, II) to assess the inter-rater reliability of a test battery of functional performance, muscle strength and leg extension power on THR patients and III) to examine whether two weekly sessions of supervised PRT in combination with home-based exercise is more effective than unsupervised home-based exercise alone in improving leg-extension power of the operated leg 10 weeks after THR in patients with perceived functional limitations.

The thesis consists of three studies (I-III) including patients undergoing primary THR due to hip osteoarthritis (OA) at Silkeborg Regional Hospital in the period September 2010 to November 2012. In Study I, 146 patients treated with movement restrictions and a standard package of assistive devices (restricted group) was compared to 219 patients treated with less movement restrictions and use of assistive devices according to individual needs (unrestricted group) in a non-randomised, comparative study. Questionnaires on function, pain, quality of life (HOOS), anxiety, depression (HADS), working status and patient satisfaction were completed before THR, 3 and 6 weeks after. At the 3-week follow-up independency in four different activities of daily living (ADL) tasks was evaluated. In Study II, two raters performed test and re-test on two samples of 20 patients 3 months after THR. The test battery included sit-to-stand performance, 20-metre maximum walking speed, stair climb performance, isometric muscle strength (hip abduction/flexion), and leg extension power. In Study III, patients were randomly assigned to a control group (n=30) performing home-based exercises 7 days/week or an intervention group (n=32) performing PRT 2 days/week and home-based exercises the remaining 5 days/week. The PRT consisted of four lower extremity exercises performed with loads of 8-12 repetition maximum (RM) from week 1 to 10 after THR. Outcome was assessed before THR and 10 and 26 weeks after by the test battery presented in Study II and patient-reported outcome (HOOS). The primary outcome was change in leg extension power from baseline to 10-week follow-up.

Study I showed slightly slower recovery in patient-reported function in the unrestricted group compared to the restricted group, but the difference was
eliminated after 6 weeks and potentially biased by missing answers. The unrestricted group was more independent in ADL after 3 weeks and returned earlier to work compared to the restricted group, with no differences in the other patient-reported outcomes. The reliability study (II) documented acceptable relative and absolute inter-rater reliability of the test battery on a group level, but not on an individual level. In Study III, the supervised PRT in addition to home-based exercise was not superior to home-based exercise alone in improving leg extension power of the operated leg after THR. A few secondary outcomes favoured PRT but seemed clinically insignificant.
2. Danish summary

Total hoftealloplastik (THA) operation fører til betydelig smertelindring og forbedring af funktionsniveauet. Der er dog vedvarende deficits i muskelstyrke og fysisk funktionsevne efter operationen. Progressiv styrketræning påbegyndt tidligt efter THA kan potentielt reducere disse deficits og dermed forbedre kvaliteten af rehabiliteringen. Traditionelt har rehabilitering efter THA indbefattet bevægerestriktioner for at forebygge hoftelukation. Forbedringer i operationsteknik og brugen af større ledhoveder har muligvis ændret rationalet for disse restriktioner.

Formålene med denne ph.d. afhandling var, I) at undersøge betydningen af bevægerestriktioner og brugen af hjælpemidler på rehabiliteringen efter fast-track THA, II) at bestemme inter-tester reliabiliteten af et testbatteri til måling af funktionsevne, muskelstyrke og ekstensionskraft i benet hos patienter der er opereret med THA og III) at undersøge om progressiv styrketræning to gange ugentligt i kombination med hjemmetræning er mere effektivt end ikke-superviseret hjemmetræning alene til at forbedre ekstensionskraften i det opererede ben 10 uger efter THA hos patienter med selv-vurderede funktionsbegrænsninger.

var ændringen i ekstensionskraft i det opererede ben fra præoperatvet til 10 uger postoperatvet.

3. Introduction

3.1 Total Hip Replacement

Total hip replacement (THR) is primarily offered to patients with end-stage osteoarthritis (OA) to reduce pain and improve function.\(^1\) The effect of THR is well documented; the majority of the patients experience significant pain relief and functional improvements and are very satisfied with the procedure.\(^2\)-\(^7\) The procedure is so effective, that THR has been termed the surgery of the century in *The Lancet*.\(^8\)

The surgical procedure involves removal of cartilage and bone from the femoral head and acetabulum and replacing it with artificial joint components: a stem inserted into the femoral bone with a ball on the top and an artificial socket with a polyethylene liner inside the acetabulum (see Figure 1).

Figure 1. Total hip replacement: artificial joint components and position in the pelvis and femoral bone.

![Image of total hip replacement](Protesekompagniet (Depuy Synthes).)

The era of THR surgery as it is known today began in the 1960s when Sir John Charnley introduced THR with the prosthetic implant fixated to the bone by cement and was the first to demonstrate long-term success.\(^9\) Since then, numerous studies have investigated different materials, designs and surgical methods to optimise the outcome and longevity of THR. The prosthetic survival rates in Denmark demonstrate that 92\% of the implants are still functioning 10 years after THR and 84\% after 17 years.\(^10\) The most common indication for THR is OA, which is the cause for 79\% of the operations. Other indications are femoral fractures, femoral head necrosis, congenital hip disorders, and rheumatoid arthritis.\(^10\) Currently more than 8000 primary THR and more than 1400 revision THRs are performed annually in...
Denmark – and the incidence is increasing due to a longer lifespan and a general expectation of having an active lifestyle, even in old age. The posterior approach is most commonly used especially in Denmark, with 95% of the THR surgeries being performed using the posterior approach. At Silkeborg Regional Hospital, the implants used are predominantly metal stems articulating with polyethylene liners as is most commonly used in Denmark. When patients are below 75 years of age, cementless prostheses are primarily used, and for the older patients cemented prostheses are primarily used.

3.2 Fast-track surgery
During the last decade, an increasing focus has been on fast-track surgery (also called enhanced recovery programme) aimed at gaining rapid functional recovery, as well as reduced hospital stay and reduced postoperative morbidity through evidence-based optimisation within all areas of patient management. These areas include pre-operative patient education, peri-operative pain management (including spinal anaesthesia), reduction of surgical stress response, optimal nutrition, early mobilisation, well-adjusted blood management and thromboembolic prophylaxis. The fast-track concept involves implementing well-described pathways for these procedures, which often requires a revision of the organisational factors. Thus, adoption of multimodal pathways by dedicated elective centres has been suggested. The outcomes after fast-track THR have demonstrated substantial reduction in length of stay, with no increase in readmission rates and with subsequent high patient satisfaction at lower health care costs. Fast-track programmes including mobilisation on the day of surgery instead of the day after decreases length of stay and results in lower pain scores. Well-described functional discharge criteria are crucial within the fast-track concept to assure that the timing of hospital discharge depends on functional recovery rather than routines at the department and organisational factors at the hospital. At the Elective Surgery Centre (former Department of Orthopaedic Surgery) at Silkeborg Regional Hospital, a fast-track methodology was implemented in 2004, at first for a subgroup of THR patients with a family relative joining them during 5 days of hospital admission (known as the Joint Care concept) and from 2006 this was reduced to 3 days. Since 2010, all THR surgeries have been performed in a fast-track setup, with admission on the day of surgery and 1-2 days of postoperative hospitalisation.
3.3 Recovery after THR

As described earlier, undergoing THR surgery results in substantial pain reduction and gains in quality of life and function. Nevertheless, there are some deficits documented in the literature: unfavourable long-term pain outcome in 7-23% of patients, deficits in lower extremity muscle strength, deficits in functional capacity, long-term deficits in perceived function and inactive lifestyle.

3.3.1 Function

It is well established in the literature that perceived function and functional performance reflect different aspects of functioning. A definition of these aspects of functioning is given in Table 1 and used throughout this thesis.

Table 1. Different aspects of functioning

<table>
<thead>
<tr>
<th>Aspects of functioning</th>
<th>Meaning</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived functiona</td>
<td>How impaired the patients feel</td>
<td>Patient-reported outcome questionnaires</td>
</tr>
<tr>
<td>Functional performanceb</td>
<td>What the patients can actually do</td>
<td>Performance tests, for example: Walking test, chair rise test, stair test, timed-up-and go</td>
</tr>
<tr>
<td>Daily activity</td>
<td>What the patients actually do in their daily life</td>
<td>Directly measured by accelerometers, pedometers etc. Indirectly measured by questionnaires or activity diary</td>
</tr>
</tbody>
</table>

aAlso termed patient-reported function, bAlso termed functional capacity and physical function

The pace of recovery differs significantly between different outcome measurements, as illustrated in Figure 2. Pain and perceived function improves rapidly, with significant improvement from preoperative already within the first week after THR. Physical performance, as measured with tests of muscle strength or functional performance, decreases early after THR and reaches preoperative levels within 1 to 3 months after surgery. Concerning actual daily activity (what the patients actually do), the literature is sparse. It seems that THR patients reach their preoperative level of activity within 3 months after surgery. A recent systematic review indicates that 8 months after surgery, THR patients have recovered to about 80% of the levels of healthy controls in all three aspects of functioning, but it remains unclear whether and when patients fully recover to the level of controls. There seems to be consensus that it is crucial to include measurements of both perceived function and functional performance when evaluating functional outcome after THR due to the distinct discrepancy between these, functional performance recovery being less and latest to occur.
Figure 2. Illustration of the pace of recovery in different aspects of functioning (Figure constructed on the basis of the literature covered in section 3.3)

3.3.2 Muscle strength

Hip muscle strength is reduced in patients with hip OA compared to the contralateral leg and to healthy controls.\textsuperscript{33, 34} THR surgery leads to further acute loss of muscle strength,\textsuperscript{27} potentially caused by post-surgical catabolism,\textsuperscript{35} immobilisation,\textsuperscript{36} diminished neural drive to muscle fibres\textsuperscript{36} and arthrogenic muscle inhibition (AMI).\textsuperscript{37} AMI is a well-known phenomenon in knee surgery that reflects failure in muscle activation close to the operated joint possibly due to intra-articular swelling, inflammation, pain and structural joint damage. AMI may appear after hip surgery as well.\textsuperscript{38} Recent reports indicate that hip muscle strength is significantly decreased 1 month after surgery but regained within 3 months. (Figure 2).\textsuperscript{18, 20} However, THR patients experience prolonged muscle weakness up to 2 years after surgery compared to healthy controls, especially in hip flexion and abduction.\textsuperscript{19, 39} Likewise, substantial between-limb asymmetry in hip muscle strength has been documented to be present during the first 6 months after THR, and these deficits persist in some muscle groups up to 1 year, primarily in hip flexion.\textsuperscript{18} These studies on post-surgical muscle strength have presumably included THR patients undergoing conventional surgical procedures; at least fast-track procedures are not reported. A few recent reports suggest less muscle strength loss and significant strength increases from preoperative levels within 3 months after fast-track THR.\textsuperscript{29, 30}
3.4 Rehabilitation after THR

3.4.1 Movement restrictions and use of assistive devices

Hip dislocation is a rare but severe complication after THR, and studies have reported dislocation rates of ~0.5 to 4.5% after THR performed through the posterior approach.\textsuperscript{15, 40, 41} A multitude of factors contribute to dislocation after THR, including component malposition, patient education, femoral head size and preoperative range of motion (ROM).\textsuperscript{42-45} Rehabilitation during the initial months after THR, when the risk of dislocation is greatest, has traditionally included many restrictions on hip range of motion and patient activity as a preventive measure.\textsuperscript{42, 46, 47} The movement restrictions typically include maximum 90° of hip flexion and no adduction and internal rotation beyond the neutral position. To comply with these restrictions, patients are often provided with assistive devices such as elevated toilet seats, elevated chairs (or wedge pillows), abduction pillows and ergonomic reachers. Activity restrictions include driving a car and sleeping on the side. Such restrictions are often applied the first 1-3 months postoperatively.\textsuperscript{42, 46} Improvements in surgical techniques and increase in the femoral head size of the hip implants have decreased the risk of hip dislocation,\textsuperscript{48} and this may have changed the rationale for these restrictions.\textsuperscript{49} Studies including patients undergoing THR performed through the anterolateral surgical approach demonstrate continuously low dislocations rates when movement restrictions are eliminated or reduced (Table 2).\textsuperscript{46, 47, 49, 50} Furthermore, some of these studies have demonstrated benefits of less restricted rehabilitation in terms of earlier ambulation, higher patient satisfaction and earlier return to work.\textsuperscript{46, 47} As shown in Table 2, the literature concerning THR using the posterior approach is sparse; only conference abstracts or small-sample studies have compared restricted versus unrestricted rehabilitation. The only peer-reviewed article reports better patient reported outcome (PRO) using no restrictions in combination with enhanced physiotherapy.\textsuperscript{31} In that study, only patients with hip resurfacing implants were included; thus applying the results to standard THR might be inappropriate.\textsuperscript{31} The positive findings they report could be caused by enhanced physiotherapy interventions as well as unrestricted movements, and their sample size is too small to reach any conclusion regarding dislocations risk. The study by Skettrup \textit{et al.}\textsuperscript{51} is not powered to conclude concerning risk of dislocations, they find neither benefit nor harm of unrestricted rehabilitation on patient-reported outcomes and functional performance. Gromov \textit{et al.}\textsuperscript{52} reports comparable hip dislocation rates with and without movement restrictions (3.4% versus 3.1%) in a retrospective trial on a larger sample. But, these conference abstracts should be interpreted with caution in light of their unpublished status. Thus, the possible benefits or harm of unrestricted rehabilitation after THR using the posterior surgical approach remains unknown.
Table 2: Studies regarding rehabilitation with or without movement restrictions after THR using the anterolateral or posterior surgical approach

<table>
<thead>
<tr>
<th>Study</th>
<th>Design / n</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Dislocations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Posterior surgical approach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barker, 2013</td>
<td>RCT / 80</td>
<td>+/- precautions and enhanced rehab</td>
<td>1 year</td>
<td>0%</td>
<td>Accelerated rehab + no restrictions→↑PRO</td>
</tr>
<tr>
<td>Gromov, 2013</td>
<td>Retrospective / 985 + 685</td>
<td>+/- precautions</td>
<td>3 months</td>
<td>3.4% / 3.1%</td>
<td>No restrictions→dislocation rate</td>
</tr>
<tr>
<td>Skettrup, 2011</td>
<td>RCT / 80</td>
<td>+/- restrictions</td>
<td>3 months</td>
<td>0%</td>
<td>No restrictions →dislocations →function</td>
</tr>
<tr>
<td><strong>Anterolateral surgical approach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrepo, 2011</td>
<td>Cohort / 2,532</td>
<td>- restrictions</td>
<td>6 months</td>
<td>0.15%</td>
<td>Low dislocation rate with no restrictions</td>
</tr>
<tr>
<td>Ververelli, 2009</td>
<td>RCT / 81</td>
<td>+/- restrictions</td>
<td>1 year</td>
<td>0%</td>
<td>No restrictions →dislocations + earlier ambulation</td>
</tr>
<tr>
<td>Peak, 2005</td>
<td>RCT / 265</td>
<td>↑/↓ restrictions</td>
<td>6 months</td>
<td>0.66% / 0%</td>
<td>Less restrictions→dislocations ↑satisfaction + earlier return to work</td>
</tr>
<tr>
<td>Talbot, 2002</td>
<td>Cohort / 499</td>
<td>- restrictions</td>
<td>6 weeks</td>
<td>0.6%</td>
<td>Low dislocation rate with no restrictions</td>
</tr>
</tbody>
</table>

PRO: Patient reported outcome, → comparable, ↑ many/increase, ↓few/decrease

### 3.4.2 Exercise therapy after THR

One of the first studies to investigate the effect of exercises after THR was Sashika et al in 1996. In a non-randomised controlled study initiated ½-2 years after THR, they found a 6 week home-based exercise program with strengthening exercises effective in improving hip abduction strength compared to a control group with no prescribed exercises. Since then, numerous studies have been published on the subject postoperative exercise in relation to THR. In Table 3, randomised controlled trials investigating efficacy of postoperative exercises on muscle strength, functional performance and/or PRO are listed.
<table>
<thead>
<tr>
<th>Study</th>
<th>n (THR)</th>
<th>Comparison†</th>
<th>Training initiation</th>
<th>Training dosage</th>
<th>Intervention focus</th>
<th>Blinding/ Follow-up</th>
<th>Effect on primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monticone, 2014⁵⁴</td>
<td>100</td>
<td>Supervised functional exe + weight bearing vs ROM exe</td>
<td>4-7 days post THR</td>
<td>90 min x 5/week for 3 weeks</td>
<td>Function, balance, ↓use of walking aids</td>
<td>Yes / 1 year</td>
<td>↑PRO</td>
</tr>
<tr>
<td>Heiberg, 2012²⁵</td>
<td>68</td>
<td>+/- Supervised group-based functional exe</td>
<td>3 months post THR</td>
<td>70 min x 2/week for 6 weeks</td>
<td>Neuromuscular functional exe</td>
<td>Yes / 1 year</td>
<td>↑Walking distance</td>
</tr>
<tr>
<td>Liebs, 2012⁵⁶</td>
<td>465 (280)</td>
<td>Supervised early vs late aquatic exe</td>
<td>6 days vs 14 days post THR</td>
<td>30 min x 3/week until 5 week post THR</td>
<td>Proprioception, coordination, strength*</td>
<td>Unspecified / 2 year</td>
<td>→PRO</td>
</tr>
<tr>
<td>Mikkelsen, 2012 (pilot study)³⁰</td>
<td>44</td>
<td>Home-based rubber band vs no resistance exe</td>
<td>1 day post THR</td>
<td>Daily for 12 weeks</td>
<td>Strength*, function</td>
<td>Yes / 12 week</td>
<td>→Walking speed</td>
</tr>
<tr>
<td>Aprile, 2011 (pilot study)⁵⁷</td>
<td>27 (15 THR)</td>
<td>Supervised group-based vs individual</td>
<td>3 weeks post THR</td>
<td>1-2 h daily for 15 days</td>
<td>Proprioception, strength*, flexibility</td>
<td>Yes / 15 days</td>
<td>→PRO</td>
</tr>
<tr>
<td>Liebs, 2010⁵⁸</td>
<td>362 (203)</td>
<td>+/- Stationary bike during rehab</td>
<td>2 weeks post THR</td>
<td>3 times/week ≥ 3 weeks</td>
<td>Stationary bike at low intensity</td>
<td>Unspecified / 2 year</td>
<td>↑PRO</td>
</tr>
<tr>
<td>Giaquinto, 2010⁵⁹</td>
<td>64</td>
<td>Hydrotherapy vs land-based exe</td>
<td>&lt;10 days post THR</td>
<td>40 min x 6/week for 3 weeks</td>
<td>Gait in water (unspecified)</td>
<td>Yes / 6 months</td>
<td>↑ PRO</td>
</tr>
<tr>
<td>Husby, 2010⁶⁰ + Husby, 2009⁶¹</td>
<td>24</td>
<td>+/- Strength training</td>
<td>1 week post THR</td>
<td>1 hour x 5/week for 5 weeks</td>
<td>Strength training at 5 RM</td>
<td>Unspecified / 1 year</td>
<td>5 week: ↑Mm strength. 1 year: →Mm strength →PRO</td>
</tr>
<tr>
<td>Stockton, 2009⁶²</td>
<td>57</td>
<td>2 vs 1 daily physiotherapy session</td>
<td>1 day post THR</td>
<td>Daily for ~ 8 days</td>
<td>Mobilisation + transfer</td>
<td>Partly /6 days</td>
<td>↑ADL independency at day 3 not day 6</td>
</tr>
<tr>
<td>Rahmann, 2009⁶³</td>
<td>65 (27)</td>
<td>Supervised aquatic vs land-based exe</td>
<td>4 days post THR</td>
<td>Daily for 14 days</td>
<td>Function and strength*</td>
<td>Yes / 14 days</td>
<td>↑Mm strength → function</td>
</tr>
</tbody>
</table>

Abbreviations: Exe: exercise, vs: versus, ROM: Range of motion, PRO: Patient reported outcomes, ADL: Activities of daily living, RM: Repetition Maximum, Mm: muscle, † Intervention group mentioned first, *No information on training load, → comparable, ↑ increase, ↓ decrease
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Comparison†</th>
<th>Training initiation</th>
<th>Training dosage</th>
<th>Intervention focus</th>
<th>Blinding / Follow-up</th>
<th>Effect on primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suetta, 200864 + Suetta 2004a+b65, 66</td>
<td>30</td>
<td>Strength training vs electrical mm stimulation vs home-based exe</td>
<td>~1 week post THR</td>
<td>Strength training 3 days/week for 12 weeks</td>
<td>Quadriceps muscle strength at 20 to 8 RM</td>
<td>Yes /12 week</td>
<td>▲Mm strength, ▲Mm size ▼hospitalisation, ▲function</td>
</tr>
<tr>
<td>Gremeaux, 200867</td>
<td>29</td>
<td>+/- electric mm stimulation</td>
<td>&lt; 2 weeks post THR</td>
<td>1 hour x 5/week for 5 weeks</td>
<td>Electrical stimulation quadriceps + calf mm</td>
<td>Unspecified /45 days</td>
<td>▲Mm strength</td>
</tr>
<tr>
<td>Smith, 200968</td>
<td>60</td>
<td>+/- bed exe</td>
<td>1 day post THR</td>
<td>Daily for 6 weeks</td>
<td>ROM + static muscle exe</td>
<td>Yes /1 year</td>
<td>6 week + 1 year: →ADL independency, →PRO</td>
</tr>
<tr>
<td>Galea, 200869</td>
<td></td>
<td>Supervised vs home-based exe</td>
<td>1 day post THR</td>
<td>Daily + in centre 45 min x 2/week for 8 weeks</td>
<td>Functional tasks + individual progression</td>
<td>Unspecified /8 week</td>
<td>→PRO, →function</td>
</tr>
<tr>
<td>Unlu, 200770</td>
<td>26</td>
<td>Supervised vs home-based exe vs walking</td>
<td>1-2 years post THR</td>
<td>2 times/days for 6 weeks</td>
<td>ROM + low intensity strength (10-30% of max) vs only walk</td>
<td>Yes /6 weeks</td>
<td>▲Mm strength</td>
</tr>
<tr>
<td>Trudelle-Jackson, 200471</td>
<td>28</td>
<td>Home-based strength + stability vs ROM + isometric exe</td>
<td>4-12 months post THR</td>
<td>3-4 times/week for 8 weeks</td>
<td>Weight bearing + strength* + stability</td>
<td>Yes /8 week</td>
<td>▲PRO ▲Mm strength</td>
</tr>
<tr>
<td>Jan, 200472</td>
<td>53</td>
<td>Home-based exe vs no intervention</td>
<td>&gt;1.5 years post THR</td>
<td>Daily exe + 30 min walk for 12 week</td>
<td>ROM + hip strength* + walk</td>
<td>No /12 week</td>
<td>→Mm strength (↑ in per-protocol analysis)</td>
</tr>
<tr>
<td>Hesse, 200373</td>
<td>80</td>
<td>+/- Treadmill training</td>
<td>~ 3 weeks post THR</td>
<td>45 min/day for 10 days</td>
<td>Treadmill walking</td>
<td>Yes /1 year</td>
<td>▲Harris hip score (&gt;60% drop out at 1 year)</td>
</tr>
<tr>
<td>Jesudason, 200274</td>
<td>42</td>
<td>+/- bed exe</td>
<td>1 day post THR</td>
<td>2-3 times/day for 7 days</td>
<td>ROM</td>
<td>Yes /7 days</td>
<td>→ADL independency</td>
</tr>
</tbody>
</table>

Abbreviations: Exe: exercise, vs: versus, ROM: Range of motion, PRO: Patient reported outcomes, ADL: Activities of daily living, RM: Repetition Maximum, Mm: muscle, † Intervention group mentioned first, *No information on training load, → comparable, ↑ increase, ↓ decrease
In Table 3, 22 papers are briefly described representing 19 studies. In general the existing exercise intervention studies clearly indicate beneficial effects of training after THR. However, there are several shortcomings to the design, scientific methodology, sample size and intervention descriptions in a number of the studies.

Several studies have investigated the effect of additional training interventions or intensifying traditional interventions.\textsuperscript{30, 54, 55, 58, 60-62, 64-68, 71-74} The majority of these report superior effect of more training/higher intensity on perceived function, muscle strength or functional performance.\textsuperscript{54, 55, 58, 60-62, 64-67, 71, 73} However, adding low intensity bed exercises in the early rehabilitation did not provide additional effects.\textsuperscript{68, 74} Two studies did not prove additional effects of intensifying or adding exercises to existing rehabilitation.\textsuperscript{30, 72} The study by Mikkelsen \textit{et al} is a pilot study\textsuperscript{30} and the study by Jan \textit{et al}\textsuperscript{72} reported low compliance and did find effect of the intervention in a per-protocol analysis. Especially interventions aiming at increasing muscle strength seems appropriate since muscle strength is markedly reduced early after surgery, and persisting deficits have been documented as described in section 3.3.2. Often strengthening exercises are reported with no information on training load, as marked with * in Table 3. Likewise, information on progression and dose are often lacking as well as the description of the regime in the control groups.

Some studies in Table 3 compare different settings, timing or delivery type of exercises.\textsuperscript{56, 57, 59, 63, 69, 70} There seems to be no differences when comparing outpatient to home-based exercise\textsuperscript{69, 70} or group-based to individual exercise\textsuperscript{57} or early initiation (day 6) to late initiation (day 14) of exercise.\textsuperscript{56} However, two studies indicate water-based exercises to be superior to land-based exercise.\textsuperscript{59, 63}

The timing of the training interventions in the studies vary between immediate start-up after surgery to initiation of training interventions years after THR (Table 3). Bandholm & Kehlet suggest that exercise therapy after fast-track THR should be initiated early after surgery, before the most pronounced decline in muscle strength and function appears.\textsuperscript{75} Nonetheless, it seems reasonable to conclude that intensifying exercises and/or adding exercises in the rehabilitation after THR have a beneficial effect on perceived function, muscle strength or functional performance. However, it remains unknown weather this applies after fast-track THR as well, since none of the studies specifically reports the participants to be treated in a fast-track setup. Thus, several studies are conducted in post-discharge rehabilitation units and do not report length of stay in hospital and others report hospitalisation periods up to 10-16 days.\textsuperscript{66}
3.4.3 Progressive resistance training

The principle of progressive resistance training (PRT) is to continually increase load in the resistance exercises, thereby inducing increased stress to the muscles that respond by increasing the ability to produce strength. In order to assess and describe the relative load during PRT, the term repetition maximum (RM) is used. RM describes the maximum possible repetitions at a given load, for example 10 RM describes the heaviest load possible for 10 consecutive exercise repetitions. It is recommended to use high loads (>70% of 1 RM, corresponding to 12 RM) during resistance training in musculoskeletal rehabilitation.

In healthy older adults the effect of PRT in increasing muscle strength, power and functional performance is well documented. In recent years, PRT has frequently been applied in musculoskeletal rehabilitation, e.g. after orthopaedic surgery. A recent systematic review concludes that PRT is safe and effective in increasing muscle strength, reducing pain and improving functional performance in musculoskeletal rehabilitation, specifically after THR.

The conclusions drawn in the previous section (3.4.2) are supported by a newly published systematic review on PRT before and after total hip and knee replacement. They report a weak-to-moderate evidence of a beneficial effect of pre- and postoperative progressive resistance training interventions on muscle strength and functional capacity in THR patients. This conclusion is based on one study (two papers) investigating a peri-operative intervention with exercise before and after THR and the two studies on postoperative PRT included in Table 3.

Details regarding these two studies are reported in Table 4.
Table 4: Randomised controlled studies on postoperative progressive resistance training after total hip replacement

<table>
<thead>
<tr>
<th>Study details</th>
<th>Suetta\textsuperscript{64-66}</th>
<th>Husby\textsuperscript{60, 61}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{n (PRT group)}</td>
<td>30 (11)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Training initiation post THR</td>
<td>When possible</td>
<td>1 week</td>
</tr>
<tr>
<td></td>
<td>Median 7 days</td>
<td></td>
</tr>
<tr>
<td>Warm-up</td>
<td>10 min stationary bike</td>
<td>10 min stationary bike</td>
</tr>
<tr>
<td>Exercise</td>
<td>Leg pres</td>
<td>Leg pres</td>
</tr>
<tr>
<td></td>
<td>Knee extension</td>
<td>Hip abduction</td>
</tr>
<tr>
<td>Sets and repetitions</td>
<td>Week 1-6: 3-5 sets of 10 rep</td>
<td>4 sets of 5 rep</td>
</tr>
<tr>
<td></td>
<td>Week 6-12: 3-5 sets of 8 rep</td>
<td></td>
</tr>
<tr>
<td>Intensity</td>
<td>Week 1: 20 RM</td>
<td>Week 1-4: 5 RM</td>
</tr>
<tr>
<td></td>
<td>Week 2-4: 15 RM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 5-6: 12 RM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 6-12: 8 RM</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>3 days/week</td>
<td>5 days/week</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

**Results after intervention period (PRT versus control)**

| Muscle strength               | ↑ isokinetic quad. strength \((60°+ 180°/seconds)\) | ↑ 1RM in leg press + hip abduction, →peak force, ↑RFD |
|                              | ↑ isometric quad. strength   |                                               |
|                              | ↑RFD                          |                                               |
| Muscle size                  | ↑ cross-sectional area \((\text{muscle + muscle fiber})\) | Not measured |
| Performance tests            | ↑ Sit-to-stand test, →stair test, →walk speed, ↑Stair walking power | → gait parameters (step length, stance time) |
|                              |                               | ↑work efficiency →max oxygen consumption |
| PRO                          | Not measured                  | →SF-36                          |
|                              |                               | →hip function score              |

PRT: Progressive resistance training, rep: repetitions, Quad: Quadriceps, RM: Repetition Maximum, PRO: patient reported outcome, SF-36: Short form-36 (generic health status questionnaire), RFD: rate of force development, → comparable, ↑ increase, ↓decrease

The literature reveals that PRT can be initiated early after THR on quadriceps and hip abduction muscles and is more effective in improving muscle strength and muscle size compared to less intensive training interventions (Table 4). Concerning functional performance and PRO the results are more divergent. Due to the small sample sizes, few exercises included and inconclusive results concerning patient-reported and functional outcomes, these promising results need to be confirmed in larger studies and on additional muscle groups around the hip. As earlier mentioned also the implementation of fast-track treatment programmes makes it relevant to further investigate the efficacy of PRT after THR.
4. Objectives and hypothesis

The overall objective of this thesis was to investigate whether improvement in rehabilitation after fast-track THR can be achieved through reduced movement restrictions and less use of assistive devices and the application of supervised PRT in addition to home-based exercise. The specific objectives and hypotheses for each study are covered below.

Study I
Objective: To evaluate the influence of assistive devices and movement restrictions during early rehabilitation after fast track total hip replacement on 1) Patient-reported function, pain and quality of life, 2) Functional capacity evaluated by physiotherapists and 3) Patient-focused variables: anxiety/depression, return to work and patient satisfaction.

Hypothesis: Reduction of movement restrictions and use of assistive devices result in superior outcomes on 1), 2) and 3) during the first 6 weeks after THR.

Study II
Objective: To assess the inter-rater reliability of a proposed test battery that included four lower-extremity performance tests, two isometric muscle strength tests and one test of leg extension power in THR patients 3 months after surgery. Furthermore, the aim was to determine which is the more reliable of two commonly used sit-to-stand tests in THR patients: five repetitions sit-to-stand or 30-second sit-to-stand.

Hypothesis: The test battery shows acceptable absolute and relative reliability with intraclass correlation coefficients (ICC) above 0.80 and standard error of measurements (SEM) above 10% of the mean of the two test sessions.

Study III
Objective: To examine whether two weekly sessions of supervised progressive resistance training (PRT) in combination with five weekly sessions of unsupervised home-based exercise is more effective than seven weekly sessions of unsupervised home-based exercise in improving leg-extension power of the operated leg 10 weeks after total hip replacement (THR) in patients with perceived functional limitations.

Hypothesis: The PRT intervention results in larger improvement in leg extension power as well as in the secondary outcomes compared to the unsupervised home-based exercise.
5. Methodological considerations

5.1 Ethical issues
All the studies were conducted in accordance with the Declaration of Helsinki II, and the Danish Data Protection Agency approved the studies (Journal numbers: Study I: 2007-58-0010, studies II and III: 2010-41-4907). The Central Denmark Region Committee on Biomedical Research Ethics reviewed Study I as non-notifiable (Inquiry 41/2011) and accepted initiation of the study. The same committee approved Study II and Study III in a combined application (M-20090231). The randomised controlled trial (RCT) (Study III) was pre-registered at ClinicalTrials.gov (NCT01214954).

In Study I, all patients undergoing total hip replacement surgery in the inclusion period were asked to fill out questionnaires as part of the quality assessment in the department. Since no informed consent was obtained directly in relation to this study, the Danish Health and Medicines Authority permitted access to the patients’ medical journals (3-3013-196/1/). In Study II, patients were contacted before their scheduled 3-month postoperative outpatient visit at the hospital. They were given written and verbal information, and if they were willing to participate in the study, the tests were performed on the day of their hospital visit. In Study III, eligible patients were informed about the study during preoperative ambulant visit at the hospital, and a minimum of 2 days of consideration time was offered. Written informed consent was obtained in studies II and III.

In Study I, we found it necessary to pre-define a stopping guideline, since the safety-issues of removing movement restrictions with regard to hip dislocation were unknown. It was decided that occurrence of five hip dislocations among the first 100 patients without movement restrictions, and subsequently a dislocation rate of ≥ 5% should result in a change of the procedure.

5.2 Design of studies
The choice of study design for the three studies is described below.

In Study I, we used a non-randomised controlled design with 6-week follow-up. The study compared patients before and after implementation of a less restricted rehabilitation regimen. This comparative before-after design was chosen instead of parallel group design to avoid potential contamination of the intervention in the two groups. When hospitalised in the same department, patients will inevitably gain
knowledge of the movement restrictions in the other group, and this could affect their compliance to group assignment. Furthermore, willingness to participate in a RCT might be low due to safety issues, i.e. that patients fear dislocation, as in the study by Peak et al. where 42% of the eligible patients refused to participate. The relatively short follow-up time was chosen to augment participation and because it reflects the time-frame of the movement restrictions. The enrolment period for the study was pre-defined. The restricted group was enrolled consecutively from 3 May to 19 August 2011, hereafter the rehabilitation regimen was changed, and the unrestricted group was consecutively enrolled from 25 August to 30 November 2011. During the change of procedures, a pre-defined intermediate sample of 20 patients was excluded from the study (20 to 25 August 2011).

In Study II, we tested inter-rater reliability in an intra-day test-retest design. Inter-rater test was chosen instead of intra-rater since we anticipated that more than one rater would be required in Study III. Test-retest on the same day was chosen to eliminate the day-to-day variation. Consequently, fatigue could introduce a bias, and therefore we divided the test battery into two sections applied on two samples as an attempt to minimise this problem.

Study III was a single-blinded RCT with 6-months follow-up. We chose the RCT design since it is considered the optimal design when evaluating effects of an intervention. Block randomisation was performed to ensure a continuous flow into the PRT group. Alternate block sizes of 4-6 patients were used to avoid the option of predicting the group assignment at any time. Stratification for contralateral THR was performed to ensure an equal distribution between the groups. Sequence in permuted blocks with equal numbers of “intervention” and “control” assignments was obtained using a simple “shuffling envelope” procedure before study initiation by a secretary not otherwise involved in the study. Blinding of patients, assessors and the physiotherapists supervising in PRT would be optimal, but this is not possible with this type of intervention. We blinded the outcome assessors throughout the study and the patient and in-hospital staff during hospital admission. We chose 10-week follow-up at the primary measurement time as it reflects the immediate effect of the intervention, but a 6-month follow-up was added in order to investigate the persistence of a potential effect. Furthermore, 1-year follow-up by mailed questionnaire measured the long-term PRO.

5.3 Patients
Participants in all three studies were recruited from Elective Surgery Centre at Silkeborg Regional Hospital in the period September 2010 to November 2012. All patients followed a multimodal fast-track surgical program for THR including
patient information, spinal anaesthesia, optimised multimodal pain management, enforced mobilisation and nutrition. Patients were invited to an information day prior to surgery where they were thoroughly informed about the expected course of their operation and rehabilitation and encouraged to take active part in the treatment and rehabilitation. On the day of surgery patients were admitted to the hospital, and the surgery was performed using the posterior approach. The Moore incision was used to expose the hip joint; only standard incisions were used (no minimal incisions). Primarily, cementless prostheses were used with femoral head sizes ranging from 28 to 44 mm, with the majority being 36-40 mm (shown in Paper I). Patients were subsequently discharged to their homes when they met pre-defined functional discharge criteria: independency in gait, transfer, personal care and home-based exercise as well as sufficient pain treatment and no exceptional wound oozing. The length of hospital stay was typically 1 to 2 postoperative days.

The uniform inclusion criteria used in all three studies included primary unilateral THR for hip OA and age > 18 years. Uniform exclusion criteria were resurfacing hip implant and inability to speak or read Danish.

In addition to this, some study-specific in- and exclusion criteria were used in studies II and III as described below.

Study II: Additional inclusion criteria: 55 to 80 years of age. Additional exclusion criteria: neurological diseases, cognitive problems/dementia or major postoperative complications (e.g. infection, fracture or hip dislocation). The last being possible because patients were included 3 months after surgery. We excluded patients with specific comorbidities because this was assumed to affect the reliability due to fatigue or not understanding the instructions.

Study III: Additional inclusion criteria: preoperative HOOS activities of daily living (ADL) subscale score ≤ 67, residence within 30 km from the hospital, motivated for training twice a week for 10 weeks and absence of mental or physical conditions that would impede the intervention. Additional exclusion criteria: body mass index (BMI) >35, pre-planned supervised postoperative rehabilitation and pre-planned contralateral THR within 6 months. The geographical criterion was to decrease the need for transportation to the bi-weekly training sessions. We excluded the patients with very high BMI, because it was estimated that it would be problematic for them to use the training machines.

Due to the longevity of patient inclusion into the RCT, we chose to accept an overlap between the inclusion period in studies I and III. This was possible due to the non-
randomised design of Study I. Study I was carried out as part of the quality assessment in the department, and thereby the questionnaires were administered as standard practice for all patients undergoing THR in the inclusion period. Thus, the patients gave no informed consent to participate.

5.4 Intervention
In the following section, the interventions used in the studies are described. The rationale behind the intervention is described when considered relevant for understanding the study.

5.4.1 Study I
Patients in the restricted group (RG) underwent the traditional rehabilitation in the department including restrictions of hip movement (maximum 90° of flexion, no adduction beyond neutral position and no internal rotation) during the first 6 weeks postoperatively. To obey to these restrictions patients were provided with the following standard package of assistive devices: elevated toilet seat, shoe horn, bath bench, ergonomic reacher, sock aid and wedge pillow. The unrestricted group (UG) had no movement restrictions apart from avoiding the combination of full hip flexion, internal rotation and adduction. To illustrate this for the patients, they were advised to bend between their knees when flexing the hip, e.g. to put on shoes. In the UG, assistive devices were only distributed when needed for the patient to perform activities of daily living (ADL), e.g. if a patient could not rise from a normal toilet, an elevated toilet was lent to them. Walking devices, generally crutches, were administered to all patients in both groups, as these were not considered a device to ensure adherence to movement restrictions but solely to support the walking ability. Information on the rehabilitation regimen was provided at the information day prior to surgery and in a patient brochure concerning several aspects of the surgery, hospitalisation and rehabilitation. The contents of the information day and brochure were similar for all groups, except regarding issues concerning movement restrictions and assistive devices.

Rationale for the unrestricted regimen
As described in section 3.4.1, there is some evidence to support unrestricted rehabilitation after THR using the anterolateral surgical approach. These results cannot be directly transferred to THR patients operated via the posterior approach, but it indicates that there might be a window for improving recovery. Clinical experience and a pilot study at our department imply that movement restrictions are an issue of concern for the patients. The unrestricted regimen was developed by an interdisciplinary team with representatives from the following professions: orthopaedic surgeon, physiotherapist, nurse and occupational therapist. Handling of
the safety-issues arising with the unrestricted rehabilitation is described in the ethic section 5.1.

5.4.2 Study II
All patients were tested twice on the same day by two physiotherapists (rater A and B) with a 2-hour break between the tests. The test battery was divided into two for this reliability study to reduce the impact of fatigue due to performance of all tests twice on the same day. Thus, we performed the reliability study on two patient samples. The physiotherapists underwent training and pilot testing of the standardised test procedures before the study was initiated. Sealed envelopes were used for randomisation to rater A or rater B (1:1) as the first tester for each patient. During the second test, the rater was blinded to the results of the previous test. Sample 1 performed test-retest of each of the following tests: five repetitions sit-to-stand, 30 second sit-to-stand, stair-climb test and isometric strength test in hip abduction and flexion. Sample 2 performed the leg extension power test and a 20 meter walk test.

5.4.3 Study III
Progressive resistance training
In the intervention group (IG) patients performed biweekly sessions of supervised progressive resistance training (PRT) in combination with unsupervised home-based exercise the remaining 5 days, using the exercise program as described for the control group (CG). The PRT was initiated within the first week after surgery and performed until 10 weeks after surgery in a public fitness centre with one-to-one supervision by a physiotherapist from the department. Patients warmed up on a stationary bike for 5-10 minutes and then performed unilateral PRT of the operated leg for 30-40 minutes. The resistance exercises are illustrated in Figure 3 and consisted of hip extension, leg press (replaced by knee extension the first 5 weeks), hip flexion and hip abduction in strength training machines. The relative load was increased from 10-12 repetition maximum (RM) at commencement to 8 RM during the intervention period. The absolute training load (kilograms lifted) was adjusted on a set-by-set basis for all exercises, using contraction to failure in every set. For further details on PRT, see Paper III. The PRT was combined with 10 minutes of simple functional task exercises from week 4, consisting of walking, chair rising, one-legged stance and stair performance. In the functional task exercises the focus was on quality and symmetry in the executions of the function.
Figure 3. The exercises used in the progressive resistance training

Rationale for PRT
In section 3.4.2 the principles of PRT and the literature concerning PRT early after THR are described. However, strength deficits have been reported for muscle groups beyond those targeted in these studies, e.g. hip flexor and extensor muscles and therefore PRT should likely target these muscle groups as well to enhance recovery after THR. Hence, in Study III we included PRT exercises of all the major muscle groups surrounding the hip joint. The frequency and duration were established by balancing between feasibility and effect. However, we considered it important to limit the frequency and duration of the intervention in order to foster willingness to participate as well as compliance to the intervention, especially for those with difficulties in relation to transportation and those returning to work. We chose a relatively high intensity (> 70% of 1 RM) since it is superior to lower intensities in increasing muscle strength in older adults and during musculoskeletal rehabilitation. Power training (high-velocity exercises) appears to result in superior functional gains compared to PRT in the elderly; findings, however are inconsistent. We chose PRT at low velocities instead of power training in order to use an intervention that was comparable with the previous studies on the subject and to use the most evidence-based approach to gaining strength. It is unknown whether power training is feasible and safe early after THR. The PRT programme is further described in Paper III according to strength training descriptors as suggested by Toigo and Boutoiller. The functional task exercises were included in an attempt to optimise the transferability of strength gains into functional performance.

Home-based exercise program
In the CG, patients performed daily sessions of unsupervised home-based exercise. The exercise programme consisted of unloaded exercises in the movement directions: hip flexion, extension, abduction and knee flexion/extension. Patients were recommended to perform one set of 10 repetitions of the exercises twice a day in their maximum possible range of motion. At the outpatient visit 4 weeks after surgery, the
physiotherapist asked the patients to perform the exercises with a sports rubber band to increase the relative load in the movement directions described above. Furthermore, exercises were individually adjusted if needed, for example, if a flexion contracture was identified, muscle stretching was prescribed.

**Rationale for home-based exercise program**

The intervention in the CG reflects the standard practice at our institution. We have previously investigated the effect of intensifying these unsupervised exercises from the first postoperative day, e.g. by using rubber band resistance. In that study we found no additional effect but a higher patient satisfaction when intensifying the program. Thus in the present study, and as our standard practice, we use a pragmatic approach in which we do intensify the unloaded exercises, but only after the outpatient visit 4 weeks after surgery.

### 5.5 Outcomes

In this section, the chosen outcomes in the studies are shortly covered; the outcomes are described in more detail in the papers. The rationale for the choice of outcomes is evaluated when considered relevant.

#### 5.5.1. Baseline variables

In all three studies the following baseline variables were collected: age, gender and body mass index (BMI). In Study II, only a few baseline variables were considered relevant to report. In Study I and Study III this was supplemented with the American Society of Anesthesiologists (ASA) classification (physical status classification), length of stay in hospital, status of the contralateral hip, prosthesis type. Finally, in Study I some further baseline variables were included due to the non-randomised design and the nature of the intervention: marital status, educational level, working status and femoral head size of the prosthesis.

#### 5.5.2 Study I

In Study I, we collected data as part of the standard care for all patients undergoing THR surgery, thus it had to be outcome measures reasonable and acceptable in light of the patients not having consented to participation. The measurement times were preoperative, 3 and 6 weeks after surgery. The preoperative questionnaires were handed out to patients when they were assigned to the operation and returned prior to surgery. At 3-week follow-up, data were collected in connection with patients attending an outpatient visit at the hospital and 6 week follow-up data were conducted by mail. The primary outcome was perceived limitations in ADL measured by the ADL subscale of the hip dysfunction and osteoarthritis outcome score questionnaire (HOOS 2.0). This was chosen as the primary outcome since we
wanted to measure the perceived function and thereby whether the patients’ perception of functional constraints was affected by movement restrictions and use of assistive devices. Secondary outcomes included the remaining subscales of HOOS (except from function in sport and recreation which was considered irrelevant at this early stage after THR), and the Hospital Anxiety and Depression Scale (HADS). The HADS questionnaire was included to elucidate whether the different regimens had different effects on anxiety or depression. It was hypothesised that the unrestricted regimen might lead to less distress due to less worrying about hip dislocation and about violating the restrictions. As a simple measure of early functional capacity, an ADL evaluation (ability to perform stair climbing, getting dressed, bath/shower and house cleaning) was performed by physiotherapists 3 weeks after surgery. This approach was chosen in an attempt to include a more objective measure of what the patients could actually do (different aspects of functioning is explained in Table 1). The dislocation rate within the first 6 weeks was followed closely throughout the study, and return to work and patient satisfaction was measured by questionnaire at 6-week follow-up. For further description of the measurements, see Paper I.

5.5.3 Study II
Study II investigated the inter-rater reliability of the physical tests we planned on using in the effect study (III). For a specific description of how the tests were executed, see Paper II. The measurement time was 3 months after THR in connection with an outpatient visit at the hospital.

Leg extension power and hip muscle strength
During the test of muscle strength and power, we used a sound file with a verbal command to avoid the voice and accentuation of the rater to affect the test performance. This was chosen as a preventive measure to counteract the influence of using more than one rater.

Leg extension power was used as a proxy measure of functional performance. Leg extension power is highly correlated with functional performance and the risk of falling, and it has been used in hip OA patients and after total hip replacement. The Nottingham Power Rig (University of Nottingham Mechanical Engineering Unit, UK) was used to measure leg extension power, which was expressed as the product of force and velocity in a single-leg simultaneous hip and knee extension. The power was recorded for several pushes until a plateau was reached. A minimum of six trials to minimise learning effect, and a maximum of 12 trials to minimise fatigue were obtained, and the highest measurement in Watts (W) was used. In Figure 4 the test setup is illustrated.
Isometric hip muscle strength was tested with a hand-held dynamometer Power Track II Commander (JTECH Medical, Salt Lake City, UT, USA). Measuring muscle strength in hip abduction and flexion was chosen because previous studies have shown large deficits in these muscles groups, and they were directly trained in the PRT exercises in the intervention group in Study III. It could have been relevant to measure hip extension strength as well, but we did not manage to establish a suitable position for this test in THR patients where ROM in hip extension often are limited. Hand-held dynamometer testing of lower extremity muscle strength is suggested as a valid measurement for evaluating orthopaedic patients, and it is applied in OA patients and after total joint replacement surgery. We used standardised test procedures as described by Thorborg et al. The test was repeated until a plateau was reached, with a minimum of four tests to minimise the learning effect and a maximum of 10 to minimise fatigue. Hip abduction was measured in a supine position and hip flexion in a sitting position. In Figure 5, the test setup for isometric strength testing is illustrated.
Figure 5. Test of isometric muscle strength using hand-held dynamometer in hip abduction (left) and hip flexion (right)

Functional performance test
In all the functional performance tests, the better of two trials was used. The patients performed the tests without walking aid if it was possible and safe, and if a walking aid was considered necessary, the patients used the device they would normally use.

Walking ability is considered by the patients to be the most important functional skill to improve when undergoing THR, hence it is essential to include a measure of walking ability when evaluating functional outcome after THR. Maximum walking speed over a short distance was chosen, because it is associated with independency in ADL and considered a highly relevant task in order to participate in activities outside the home, e.g. navigate in traffic. The 20-meter walking test was used as it is a part of the Osteoarthritis Initiative and is used in recent studies on patients with hip and knee OA. Patients walked as fast as possible on a 20-meter lane that included the acceleration phase (standing start) but not deceleration (walking past end line). When measuring maximum walking speed over short distances, the 10-meter walk test is often used. We decided not to use this test because previous results on the same patient group have shown that the patients obtain fast walking speeds so rapidly that the accuracy of the test could be affected by the short time frame, and a longer walking test is suggested. This is in line with newly published recommendations for functional testing of patients with hip or knee OA, where 40 meter walk test is recommended. In this recommendation it is emphasised that maximum walking speed should be used instead of a self-selected pace. It is relevant to include a measure of gait quality, as better muscle function might positively affect the gait pattern. We did measure asymmetry during walking speed and stair testing in a subgroup of the patients in Study III using inertia measurement.
unit. However, these results will be analysed and published separately and are not included in this thesis.

Chair rise performance is an important functional skill in everyday life, and high performance is associated with independency in ADL.\textsuperscript{99, 100} As a measure of chair rise performance, two tests were included in the reliability study (II); the five repetitions sit-to-stand and the 30-second sit-to-stand test. This was to evaluate which of these tests to include in the effect study (III) as the literature at that time was inconclusive. The five repetitions sit-to-stand test was chosen because it is a part of the Osteoarthritis Initiative\textsuperscript{101} and often used in patients with hip OA and after total hip replacement.\textsuperscript{66, 94, 102} The 30-second sit-to-stand is also widely used to measure chair rise performance in patients with hip OA and after THR,\textsuperscript{89, 104-106} furthermore it is recommended to use in functional testing of patients with hip and knee OA.\textsuperscript{103}

Stair-climb performance has been suggested and used when measuring functional performance in hip OA patients\textsuperscript{107, 108} and after total hip replacement.\textsuperscript{6, 66, 109} Furthermore, it is also part of the new recommendations for functional testing of patients with hip and knee OA.\textsuperscript{103} There is no standardisation of stair tests concerning, e.g. number of steps, step heights and measurement of ascending, descending or a combination. In the present study, focus was solely on ascending stairs. It was presumed that descending stairs would be affected by balance, coordination and nervousness to a larger extent than ascending. Patients ascended nine steps (16.5 cm high) as fast as possible without using the handrail.

### 5.5.4 Study III

In Study III, the test described for Study II was used for effect evaluation. The primary outcome was defined as change in leg extension power from preoperative level to 10 weeks after surgery when the intervention period was completed. There are a few deviations in the secondary outcomes between Study II and Study III. The stair climb test was changed to a longer test, 18 steps instead of nine steps, in the RCT (Study III) on the basis of preliminary results found in the reliability study (II). It was speculated that the accuracy of the test could be affected by the short time frame (mean \textasciitilde 4 seconds). The measurement of chair rise performance was performed using a 30-second sit-to-stand test in Study III, based on preliminary findings from Study II, and the possibility to score the weakest patients, even if five repetitions was impossible (the disparity between the two chair rise tests is further described in Paper II). The choice of 30-second sit-to-stand test was validated by the recommendations for functional testing on patients with hip and knee OA published after commencement of this study.\textsuperscript{103}
When measuring strength gains after PRT, a simple approach is to use 1RM testing of the trained exercises, as done by Husby et al.\textsuperscript{60, 61} We did not use this approach, as we wanted our effect measurement to vary from the trained exercise in order to minimise the influence of improved technique attained through the exercises. By measuring leg extension power and isometric hip muscle strength, we measured whether strength gains achieved during slow, dynamic muscle contractions are transferred to these other types of muscle function.

The PRO questionnaire HOOS was used repeatedly to evaluate differences between the groups during early recovery while the intervention was on-going. Furthermore, HOOS was administered by mail 1 year after surgery as an extended follow-up beyond the period of the follow-up visits at the hospital. The HOOS questionnaire is described in section 5.5.1 and in Paper I and III. In the earliest measurements, the subscale function in sport and recreation was considered irrelevant because of the questions regarding for instance running. The immediate effect of the intervention was measured at 10-week follow-up. Furthermore, early changes and long-term follow-up measurements were conducted when considered feasible and relevant, e.g. the less demanding physical tests were performed early. The outcomes applied at the different measurement times are presented in Table 5.

Table 5. Overview of outcome measures and measurement times in Study III, primary outcome and time frame coloured blue

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 week</th>
<th>4 week</th>
<th>6 week</th>
<th>10 week</th>
<th>6 month</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg extensor power</td>
<td>X</td>
<td></td>
<td></td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking speed</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chair rise</td>
<td>X</td>
<td></td>
<td></td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stair climb</td>
<td>X</td>
<td></td>
<td></td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric hip strength</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient-reported outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOOS</td>
<td>X</td>
<td>X*</td>
<td>X*</td>
<td>X X</td>
<td>X X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Training diary (weekly)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HOOS: Hip dysfunction and osteoarthritis outcome score questionnaire, *Not including the subscale concerning function in sport and recreation.

*Rationale for primary outcome*

The leg extension power was chosen as the primary outcome because it serves as a proxy for functional performance. It was chosen over functional testing as it seems possible to standardise the power test to a larger degree, and it is potentially less influenced by habits, experience, anxiety, balance, etc. We chose to focus on functional performance rather than perceived function because PRO measures may fail to capture actual changes in functional performance as measured by functional
performance tests, and it possibly reflects pain level as much as function.\textsuperscript{21, 25, 26} However, it is considered essential that the physical testing is supplemented with measurement of perceived function.

**Process indicators**

In order to evaluate the progression in training load and occurrence of potential side effects consisting of exacerbation of hip pain, we assessed these variables closely during the first 4 weeks of training in the first 20 patients in the IG. The absolute training load was measured in kilograms (kg). For each exercise at each training session, the highest load in a completed set was used as the data point. Hip pain in the operated leg was measured using a 100 mm mechanical visual analogue scale (VAS) with endpoints of 0 mm (“no pain”) and 100 mm (“worst imaginable pain”). After the final set of an exercise, the patient scored hip pain corresponding to that experienced during the set. By default, the VAS was set at 0 mm, and the patient placed the marker according to their perceived pain. The corresponding value to the nearest mm-VAS was used at the data point.

**Exploratory subgroup analysis**

On selected baseline variables the effect of the intervention was further explored in a subgroup analysis on the primary outcome. We selected the variables age, gender, BMI and the preoperative muscle function (measured by leg extension power). These variables were chosen as they are known to influence the outcome after THR\textsuperscript{29, 110-112} and/or the response to resistance training\textsuperscript{113-115} When continuous baseline variables were used, the subgroups were defined by the median value.

**5.6 Statistics**

**5.6.1 Sample sizes**

In all studies, the significance level was set at 0.05. In Study I, we chose a power of 95\%, because of the non-randomised design, we aimed at gaining as much certainty as possible in the results. In Study II and Study III the power was set at 80\% as is most commonly used in clinical trials.

In Study I, we used data on perceived function from a Danish study comparing outcome after large-head THR with no movement restrictions to standard THR with standard movement restrictions applied.\textsuperscript{116, 117} The mean score 8 weeks after surgery were 12.7 (SD 10.3) versus 17.9 (SD 11.2), and based on expecting the same difference, we needed a sample of 121 patients in each group. The actual sample in Study I was larger than anticipated (\(n=146\) in RG and \(n=219\) in UG), because we had to pre-define the enrolment period and the date for change of procedures.
In the reliability study (II), we defined a conservative level of acceptable intra-class correlation coefficient (ICC) > 0.8. With two raters and a 95% confidence interval (CI) of ± 0.2, a sample size of 13 subjects was required. To decrease the uncertainty of the results and to increase generalisability, we decided to include 20 subjects for each sample.

In the RCT (Study III), the sample size calculation was based on earlier obtained leg extension power data from pilot testing patients 3 months after THR (mean ± SD: 1.78 ± 0.49 Watt/kg). The minimal relevant difference in effect between intervention and control group was defined as 20%, which is suggested in musculoskeletal intervention research, resulting in a required sample size of 60. Based on an expected 10-15% drop out, we aimed at including 70 patients.

5.6.2 Statistical evaluation

In all studies, the significance level was set at 0.05. The statistical analyses were performed using STATA 12.1 (StataCorp, College Station, TX, USA) software package. Data was entered in Excel 2010 (Microsoft Corporation, Redmond, WA, USA) or EpiData 3.1 (Epidata association, Odense, Denmark), depending on the complexity of data. In Study III, data were double entered and validated in EpiData, and in Study I, double entry was performed on a random subsample of 100 patients, showing low error rate (0.3%). The reliability data were entered and validated in Excel.

Normal distribution was determined using probability plots and histograms. Normally distributed data were described by means and standard deviation (SD), and data not normally distributed by medians and range or interquartile range (IQR). Simple comparison of normally distributed data between or within groups was performed using unpaired or paired t-tests, respectively. On data not normally distributed, the groups were compared using the non-parametric Wilcoxon rank-sum test. When analysing changes over more than two measurement times, the groups were compared using multivariate repeated measurement analysis of variance (MANOVA), with group and time as factors. The assumption of homogeneity in standard deviations and correlations was tested, and an approximate test allowing for heterogeneity was used when appropriate. For model validation, histograms and probability plots of the differences between measurement times in each group were inspected and approved.

Study I

The primary analysis was a comparison between the groups regarding change in HOOS function score over time (MANOVA). The remaining subscales from HOOS
were analysed identically. The functional capacity evaluation, return to work and patient satisfaction were compared using chi² test or Fisher’s exact test. The hip dislocation rates were compared between the groups using Fisher’s exact test due to the very low number of events. The baseline variables were analysed according to the type of data: dichotome or grouped variables with chi² test, normally distributed variables with unpaired t-test.

Study II
Differences in test results between the two raters were analysed with a paired t-test. In accordance with published guidelines for reporting reliability and agreement studies, reliability was investigated in terms of test–retest reliability and measurement error. The agreement between the tests was examined by Bland Altman plots. Identification of the mean difference with 95% CI and limits of agreement were included in the plots. The standard error of measurement (SEM), which represents the typical error in a single measurement, was calculated by the equation SD/√2. The minimal detectable change defined as the measure of statistically significant change between two measurements, was calculated by the equation 1.96 x √2 x SEM. For a statistically significant change between two observations to be detected, the change must be at least the minimal detectable change. SEM and minimal detectable change (MDC) are presented in actual units, but they are also expressed as a percentage of the mean of the two test sessions (grand mean), making comparisons between tests and studies possible. The relative reliability was calculated using the ICC model 2.1. The ICC is a ratio of the variance between subjects over the total variance. The ICC 2.1 is a fixed model addressing both systematic and random error. The ICC is affected by sample variability in the sense that with large variability an excellent ICC can be achieved even with a large measurement error. Thus both absolute and relative reliability are reported. Yet, ICCs are used in most comparisons between tests and between studies because of their wide-spread use and unit-less nature.

Study III
The primary analysis followed the intention-to-treat principle including all randomised participants on the primary outcome: leg extension power. Data were analysed by a mixed model with a random person level and systematic effects of time, group and the interaction between time and group. The remaining group comparisons were conducted as extended per-protocol analyses using non-missing values only (no imputations). Patients who discontinued the intervention were encouraged to participate in the follow-up test anyway, and those who accepted were included in the analyses according to their original group assignment. The groups were compared regarding changes over time on the continuous variables
using MANOVA with group and time as factors. The within-group changes between baseline and 10-week follow-up were tested using a paired t-test.

To investigate changes in absolute training loads and patient-reported disability over time, repeated measures analyses of variance (ANOVAs) with Box’s conservative correction for unstructured covariance were used. For changes in hip pain during exercise and at rest, the correspondent non-parametric Friedman’s test was used.
6. Results

In the results section, selected parts of the results from each study are presented and combined when considered appropriate.

6.1 Patient characteristics

The uniform baseline characteristics in the studies are presented in Table 6. As described in section 5.5.1, not all baseline variables were considered relevant in the reliability study (II), and additional variables are included in Paper I.

Table 6. Baseline characteristics for participants in Study I, II and III.

<table>
<thead>
<tr>
<th></th>
<th>Study I RG (n=146)</th>
<th>Study I UG (n=219)</th>
<th>Study II Sample 1 (n=20)</th>
<th>Study II Sample 2 (n=20)</th>
<th>Study III IG (n=32)</th>
<th>Study III CG (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>69.0 (10)</td>
<td>68.4 (10)</td>
<td>66.2 (8)</td>
<td>68.4 (5)</td>
<td>64.8 (8)</td>
<td>65.1 (10)</td>
</tr>
<tr>
<td>BMI (kg/m²) mean (SD)</td>
<td>27.2 (5)</td>
<td>26.5 (4)</td>
<td>27.8 (4)</td>
<td>28.0 (3)</td>
<td>27.5 (4)</td>
<td>25.4 (4)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>68 (47)</td>
<td>106 (48)</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>14 (44)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Contralateral THR n (%)</td>
<td>34 (23)</td>
<td>49 (23)</td>
<td></td>
<td></td>
<td>8 (25)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Cementless prosthesis n (%)</td>
<td>125 (86)</td>
<td>190 (87)</td>
<td>Not reported</td>
<td></td>
<td>29 (91)</td>
<td>28 (93)</td>
</tr>
<tr>
<td>ASA I n (%)</td>
<td>42 (30)</td>
<td>69 (32)</td>
<td></td>
<td></td>
<td>15 (47)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>LOS = 1 day post THR n (%)</td>
<td>98 (67)</td>
<td>173 (79)</td>
<td></td>
<td></td>
<td>22 (69)</td>
<td>20 (67)</td>
</tr>
</tbody>
</table>


6.2 Study I

We included 146 THR patients in the RG and 219 in the UG. The response rate varied between groups, variables and measurement times. The response rates in RG and UG were 83-85% and 84-88% at baseline, 71-85% and 91-96% at 3-week follow-up and 87-93% and 85-93% at 6-week follow-up. Patient inclusion and response rates are further described in Paper I.

6.2.1 Primary outcome HOOS

The primary outcome was perceived function measured by the HOOS ADL subscale. The scores at baseline, 3 and 6 weeks after surgery were (mean ± SD); RG: 43±16 – 81±14 – 83±13 compared to UG: 46±17 – 76±9 – 83±14 (p = 0.004). The RG showed the
fastest increase \((p=0.004)\). At 3-week follow-up the percentage of missing values on the HOOS ADL subscale was 29% in the RG versus 9% in the UG. In the remaining HOOS subscales, no significant differences between the groups were present (see Paper I for further description).

6.2.2 Secondary outcomes

In Table 7 the secondary outcomes are presented as dichotomous variables; some of the variables are described more comprehensively in Paper I.

Table 7. Secondary dichotomised outcomes of THR patients in the restricted group (RG) and in the unrestricted group (UG)

<table>
<thead>
<tr>
<th></th>
<th>RG ((n=146))</th>
<th>UG ((n=219))</th>
<th>(p) (Chi(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent* in ADL 3 weeks post THR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stairs</td>
<td>33% (40/122)</td>
<td>51% (103/201)</td>
<td>0.003(^F)</td>
</tr>
<tr>
<td>Getting dressed</td>
<td>40% (50/124)</td>
<td>72% (148/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bath/shower</td>
<td>68% (84/124)</td>
<td>88% (181/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>House cleaning</td>
<td>38% (47/124)</td>
<td>60% (123/205)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Outcomes at 6 week post THR

<table>
<thead>
<tr>
<th></th>
<th>RG ((n=146))</th>
<th>UG ((n=219))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to work</td>
<td>32% (12/37)</td>
<td>54% (29/54)</td>
<td>0.045</td>
</tr>
<tr>
<td>Hip dislocation</td>
<td>1.4% (2/146)</td>
<td>2.7% (6/219)</td>
<td>0.48</td>
</tr>
<tr>
<td>Satisfied/very satisfied with treatment</td>
<td>96% (132/138)</td>
<td>96% (194/202)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Abbreviations: THR: Total hip replacement, ADL: Activities of daily living. *Independent of both assistive device and help from others, \(^F\) Fisher’s exact test

Table 7 reveals that a significantly higher proportion of patients in the UG were independent in the four ADL tasks at the 3-week follow-up compared to the RG. Furthermore, a higher proportion had returned to work at the 6-week follow-up in the UG than in the RG. Hip dislocation rates and patient satisfaction was comparable between the groups.

HADS results

In Table 8, the continuous HADS results are presented in accordance with the data distribution being not normally distributed. The scale goes from 0 to 21, with scores >7 representing above normal level of anxiety/depression. In Paper I, the HADS results were dichotomised for simplicity.
Table 8. Results from Hospital anxiety and depression scale (HADS) in the restricted group \((n=146)\) and the unrestricted group \((n=219)\), values are median (IQR), (% non-responders)

<table>
<thead>
<tr>
<th></th>
<th>Restricted group</th>
<th>Unrestricted group</th>
<th>(p) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6 (3;10)</td>
<td>5 (2;8)</td>
<td>0.007</td>
</tr>
<tr>
<td>3 week</td>
<td>1 (0;3)</td>
<td>1.5 (0;4)</td>
<td>0.88</td>
</tr>
<tr>
<td>6 week</td>
<td>1 (0;4)</td>
<td>1 (0;2)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>HADS Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3 (1;6)</td>
<td>2 (0;4)</td>
<td>0.036</td>
</tr>
<tr>
<td>3 week</td>
<td>1 (0;2)</td>
<td>1 (0;2)</td>
<td>0.85</td>
</tr>
<tr>
<td>6 week</td>
<td>1 (0;2)</td>
<td>0 (0;1)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Scale range: 0-21 (0-7: normal, 8-10: mild, 11-15: moderate, 16-21: severe depression/anxiety) *Wilcoxon rank-sum test of between group difference

The level of anxiety and depression was higher in the RG at baseline compared to the UG. At the follow-up measurements there were no between-group differences.

**Assistive devices**

The amount of assistive devices handed out by the hospital was reduced by 37-79% after changing to the unrestricted regimen, with the elevated toilet seat as the assistive devices mostly reduced (presented in Paper I).

**6.3 Study II**

We included 40 THR patients in the reliability study and divided them into two samples each consisting of 20 patients.

The difference (bias) between the test results from rater A and rater B concerning the 20-metre walk test was 0.32 seconds \((p=0.03)\) and 0.18 seconds \((p=0.003)\) in the stair-climb test. In the remaining tests, no significant differences occurred, meaning that there were no systematic difference in the results from rater A and rater B.

Bland Altman plot for leg extension power is shown in Figure 6, and plots of the remaining tests are presented in Paper II.
Mean difference between raters (black line) with 95% CI (red lines) and limits of agreement (blue lines). The dotted black line, Y=0 indicates perfect average agreement.

Bland Altman plots on data from leg extension power and hip abduction showed sign of heteroscedasticity; consequently, the absolute measurement error is larger at higher scores on these measurements.

The SEM in per cent of the grand mean (SEM(\%)) ranged from 3\% to 10\%, indicating the measurement error on a group level. The MDC in per cent of the grand mean (MDC(\%)) ranged from 10\% to 27\%, indicating the measurement error on an individual level. The relative reliability measured by ICC was above 0.80 in all tests, ranging from 0.83 to 0.95. The measurement properties of the specific tests are presented in Paper II. The absolute and relative reliability of the 30-second sit-to-stand compared with five repetitions sit-to-stand was ICC: 0.88 versus 0.84, SEM(\%): 7 versus 8, MDC(\%): 20 versus 22.

6.4 Study III

In Study III, 73 THR patients were consecutively included and randomised to either IG (n=37) or CG (n=36). After randomisation, two patients in each group withdrew consent, and seven were excluded due to major events such as hip fracture and hip dislocations. None of these events were considered to be associated with the rehabilitation (presented in flowchart in Paper III). The 11 patients that did not complete the study tended to be older: mean age 70.8 (SD 9), weaker: mean leg extension power at baseline: 1.26 W/kg (SD 0.6) and more often female (64\%). We
pre-planned to include 70 patients but chose to continue inclusion until 73 participants in order to secure achievement of the estimated sample size of 30 in each group despite the drop outs.

6.4.1 Training compliance and adverse effects

The patients in the IG attended a median of 19 training session (range: 1-22) during the 10-week intervention period. The resistance training was initiated at a median of 5 (range: 4-9) days after surgery. Patients reported that they performed the home-based exercises a median of 5 (range: 0-7) days a week in the IG as prescribed and 6 (range: 0-7) days a week in the CG, where 7 days a week was prescribed.

Five patients experienced adverse effects during or after PRT sessions that were related to hypotension, sequelae after brain tumour, rupture of a haematoma and knee pain. None of these adverse effects resulted in continuing complications; however, two patients discontinued the intervention due to discomfort, but they participated in follow-up visits and are included in the analysis according to their group assignment.

6.4.2 Process indicators: Training load and pain

In Figure 7, the training load and hip pain during hip flexion exercise in the first 4 weeks of training are presented for a subgroup of the IG.

Figure 7. Absolute training load (A) and hip pain (B) during hip flexion exercise at each session during the first 4 weeks of PRT applied on 20 patients after THR. Values are mean ±SD in plot A and median (IQR) in plot B.
Training load increased over time in all the exercises, $p<0.001$ (repeated measures ANOVA), while hip pain during exercise decreased in all the four exercises ($p<0.0001$, Friedman’s test).

**6.4.3 Physical tests**

Change in leg extension power from baseline to 10-week follow-up were mean (95% CI) IG: 0.29 (0.13;0.45) and CG: 0.26 (0.10;0.42) W/kg, with no between-group difference, $p=0.79$ (mixed effect model). These changes correspond to relative improvements of 21% and 17% in the IG and CG groups, respectively. In Table 9, the results on all the physical performance tests at the three main measurement times are presented. The results from the intermediate test 4 weeks postoperatively and change-estimates from baseline to 10 week follow up are presented in Paper III.

Table 9. Results from the physical outcome measures in the intervention group (IG, $n=32$) and control group (CG, $n=30$) during 6 months’ follow-up after THR

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>10 week</th>
<th>6 month</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IG</td>
<td>CG</td>
<td>IG</td>
<td>CG</td>
</tr>
<tr>
<td>Leg extension power (W/kg)$\dagger$</td>
<td>1.44(0.6)</td>
<td>1.55(0.7)</td>
<td>1.72(0.6)*</td>
<td>1.78(0.6)*</td>
</tr>
<tr>
<td>Walking speed (seconds)</td>
<td>14.0(4.8)</td>
<td>13.6(3.5)</td>
<td>11.1(2.4)*</td>
<td>12.0(2.6)*</td>
</tr>
<tr>
<td>Hip abduction strength (Nm/kg)</td>
<td>0.82(0.3)</td>
<td>0.92(0.4)</td>
<td>1.03(0.3)*</td>
<td>1.03(0.3)*</td>
</tr>
<tr>
<td>Hip flexion strength (Nm/kg)</td>
<td>1.07(0.3)</td>
<td>1.27(0.4)</td>
<td>1.25(0.3)*</td>
<td>1.32(0.4)</td>
</tr>
<tr>
<td>Sit-to-stand test (repetitions)$\dagger$</td>
<td>11.6(3.9)</td>
<td>11.9(4.6)</td>
<td>14.4(3.9)*</td>
<td>13.1(4.3)*</td>
</tr>
<tr>
<td>Stair climb test (seconds)</td>
<td>12.8(7.9)</td>
<td>13.1(7.2)</td>
<td>9.5(3.2)*</td>
<td>10.5(4.0)*</td>
</tr>
</tbody>
</table>

Abbreviations: THR: Total hip replacement, diff: difference, W/kg: Watt/kilogram bodyweight, Nm/kg: Newton*meter/kilogram bodyweight, $\dagger$1 missing at baseline, the patient was not able to perform the test due to pain, $\star$Multivariate repeated measurement analysis, testing the difference between groups over time, $\dagger$Significant within group difference from baseline to 10 week follow-up ($p<0.05$), $\dagger$Approximate test, allowing for heterogeneity

All the physical outcomes improved significantly from baseline to 10-week follow-up in both groups, except for hip flexion strength in the CG. In maximum walking speed and stair climb performance there was significantly better improvement over time in the IG compared to the CG (Table 9).
6.4.4 Patient reported outcome HOOS

In both groups, a rapid and large improvement was seen in all the HOOS subscales, with no between group differences ($p$-value range: 0.31-0.90). Ceiling effect, defined as maximum score (100 points) in $\geq 20\%$ of patients, was present in the pain subscale at 10-week follow-up and in the other subscales at 6-month follow-up, except in the subscale sport/recreation, where ceiling effects appeared only at 1-year follow-up. In Figure 8, the results from the HOOS ADL subscale are presented; the results from the remaining HOOS subscales are presented in Paper III.

Figure 8. Results from the HOOS ADL subscale in intervention group ($n=32$) and control group ($n=30$), values are mean $\pm$ 95% CI.
6.4.5 Exploratory analysis

In Table 10, the results from the exploratory subgroup analysis are presented.

Table 10. Exploratory subgroup analysis on the primary outcome: Changes in leg extension power from baseline to 10-week follow-up, values given as means [95% CI]

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>n</th>
<th>Control</th>
<th>n</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=61)</td>
<td>0.28 [0.12;0.44]</td>
<td>32</td>
<td>0.25 [0.02;0.48]</td>
<td>29</td>
<td>0.82</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=25)</td>
<td>0.37 [0.16;0.59]</td>
<td>14</td>
<td>0.001 [-0.24;0.24]</td>
<td>11</td>
<td>0.019</td>
</tr>
<tr>
<td>Male (n=36)</td>
<td>0.21 [-0.04;0.46]</td>
<td>18</td>
<td>0.40 [0.06;0.75]</td>
<td>18</td>
<td>0.35</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.28 [-0.41;1.02]</td>
<td>17</td>
<td>0.21 [-0.86;1.37]</td>
<td>13</td>
<td>0.73</td>
</tr>
<tr>
<td>≥65</td>
<td>0.29 [-0.86;1.24]</td>
<td>15</td>
<td>0.29 [-0.78;1.27]</td>
<td>16</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline leg extension power</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 W/kg</td>
<td>0.46 [-.13;1.24]</td>
<td>17</td>
<td>0.51 [-.38;1.37]</td>
<td>13</td>
<td>0.79</td>
</tr>
<tr>
<td>≥1.5 W/kg</td>
<td>0.08 [-.86;1.02]</td>
<td>15</td>
<td>0.04 [-.86;1.36]</td>
<td>16</td>
<td>0.85</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26 kg/m²</td>
<td>0.28 [-0.08;0.65]</td>
<td>11</td>
<td>0.15 [-0.17;0.46]</td>
<td>19</td>
<td>0.56</td>
</tr>
<tr>
<td>≥26 kg/m²</td>
<td>0.28 [0.09;0.47]</td>
<td>21</td>
<td>0.45 [0.09;0.81]</td>
<td>10</td>
<td>0.33</td>
</tr>
</tbody>
</table>

The subgroup analysis revealed a significant effect of the intervention among women with an opposite, yet insignificant, effect among men. The remaining subgroups showed no significant effects.
7. Discussion

7.1 Key findings

Study I
The patients in the RG group attained more rapid improvement than those in the UG group with regard to the primary outcome: patient-reported function measured by the HOOS ADL subscale \((p=0.004)\). However, the validity of the results is uncertain due to a large and potentially non-random proportion of missing answers in the RG group, 29\% versus 9\% in the UG, at the 3-week follow-up when the between-group difference occurred.

Study II
The proposed test battery showed acceptable relative and absolute inter-rater reliability on a group level, with measurement errors of 3-10\%, but not on an individual level, with MDCs of 10-27\%. The relative reliability was excellent in the entire test battery, with ICCs above 0.8. The absolute and relative reliability of 30-seconds sit-to-stand was slightly better than the five repetitions sit-to-stand.

Study III
The main finding was no superior effect of two weekly sessions of supervised PRT in addition to five weekly sessions of unsupervised home-based exercise in improving leg extension power of the operated leg 10 weeks after surgery, when compared to seven weekly sessions of unsupervised home-based exercise in patients with THR who had lower pre-operative function. All secondary outcomes improved significantly from baseline to 10-week follow-up in both groups, except with regard to hip flexion muscle strength in the CG (Table 9). There was a statistically significant difference between groups over time in maximum walking speed \((p=0.008)\) and stair climb performance \((p=0.04)\) (Table 9). We question the clinical relevance of these findings because of the small differences and the diminishing of the effect after 6 months. In all the remaining secondary outcomes, there was no between group differences over time \((p>0.05)\).
7.2 Less restricted rehabilitation (Study I)

7.2.1 Perceived function in relation to response rates
The result with regard to perceived function was surprising, since we hypothesised that fewer restrictions would result in less perceived functional limitations. At the 3-week follow-up there was a substantial difference in response rate between groups and variables. This is partly explained by less attendance at the ambulant visit 3-weeks after surgery in the RG group, which we speculate could be related to the movement restrictions and extensive use of assistive devices, but the cause of non-attendance remains unknown. However, there was an additional number of missing answers specific on the HOOS ADL subscale in the RG group, with 29% missing, whereas the subscale QOL had only 18% and the functional evaluation only 15%. In the UG group, the numbers of non-responders on the HOOS ADL subscale was only 9%. This suggests that the nature of the questions is part of the explanation. If a patient has movement restrictions, it might be difficult to answer questions concerning activities like “rising from a chair” or “reaching to the floor”. If the missing answers are non-random, e.g. among the patients with more severe conditions as shown in other studies, the result would overestimate the difference. We consider the difference found on the HOOS ADL subscale at the 3-week follow-up to be clinically insignificant and potentially invalid due to the missing answers, the difference being below 5 points, and the diminished difference after 6 weeks. This is supported by the results on the remaining HOOS subscales with less missing values in which no significant differences between groups occurred. In future studies on movement restrictions, we suggest that a physical performance test might be a better functional measure than patient-reported outcomes due to these response problems. Before commencement of this trial, we considered use of the patient-reported outcomes to be an advantage, since it could reveal how limited the patients felt, when for instance they had to use an assistive device to perform a functional task. Conversely, our results indicate that instead of reflecting these limitations, the patients tend to not answer these questions.

7.2.2 Secondary outcomes
We found significant results in favour of the UG on the secondary outcomes concerning functional capacity ($p<0.005$) and return to work ($p=0.045$). It seems that reducing movement restrictions and the use of assistive devices can lead to an earlier independent ambulation in the four ADL tasks measured in Study I. This difference between the groups can be caused by less movement restrictions and less use of assistive devices; it is not possible to distinguish between these effects. Some caution should be taken in the interpretation due to the unblinded assessment of functional capacity; however, the evaluation was standardised and kept very simple to avoid
assessor influence. Patient satisfaction was comparable between groups, indicating that the unrestricted regimen did not affect the perceived quality of the treatment when evaluated 6 weeks after surgery. The RG had a higher score of both anxiety ($p=0.007$) and depression ($p=0.036$) at baseline compared to the UG (Table 8). This difference can be caused by the preoperative information because the restricted group was informed about movement restrictions and the use of assistive devices to prevent hip dislocation. After surgery, there were no between-group differences and a very low level of anxiety and depression occurred in both groups (Table 8). Even though median values were low, this finding corresponds to 30-38% having above normal level of anxiety and 10-13% above normal level of depression before scheduled THR surgery, indicating that this could be a topic of concern (Paper I).

There are safety concerns when implementing the unrestricted regimen with regard to the risk of hip dislocation. We found comparable hip dislocation rates in the two groups; 1.4% in RG versus 2.7% in UG, $p=0.48$. This indicates that the unrestricted regimen could increase the dislocation risk, but the study is underpowered to draw any conclusions concerning dislocation risk. Thus, it remains crucial to determine the safety of unrestricted rehabilitation in relation to risk of hip dislocation in THR using the posterior surgical approach.

The number of assistive devices handed out by the hospital was markedly reduced (37-79%) after implementation of the unrestricted regimen. This is considered a component of the intervention (individual evaluation of patients need for assistive devices in combination with reduced movement restrictions) rather than a result. But it is highly relevant for clinical practice that it seems reasonable to individually evaluate the patients need for assistive devices rather than using standard packages.

**7.2.3 Comparison with relevant findings from other studies**

Apart from perceived function, the results in Study I are in line with earlier studies indicating better or equal outcomes after less restricted rehabilitation after THR using the anterolateral surgical approach.46, 47, 49, 50 The hip dislocation rates in the present study (1.4 and 2.7%) are comparable to findings from a large sample of THR performed with fast-track programmes for peri-operative care (3.5%),15 and to the unpublished, retrospective Danish study (Table 2) showing hip dislocation rates of 3.4% with movement restrictions and 3.1% without.52 However, prospective large-scale studies are needed to confirm the safety of unrestricted rehabilitation after THR using the posterior approach in relation to risk of hip dislocation.

We found a large and rapid recovery on perceived function in both groups as measured by the HOOS ADL subscale. A recent study by Barker et al,31 found greater gains in the HOOS ADL score after enhanced recovery that included no hip precautions compared to conventional rehabilitation with hip precautions in a
sample of hip resurfacing patients. They improved from baseline score ~50 in both groups to 6 weeks postoperatively ~70 and ~80, respectively. In our sample both groups had lower scores at baseline and improved more than in their study: 43 and 46 at baseline improved to 83 after 6 weeks in both groups.

7.3 Inter-rater reliability of physical tests (Study II)

The presented systematic differences between raters are considered small and clinically irrelevant (0.3 and 0.18 seconds). We found overall acceptable relative reliability and measurement errors on a group level, as expected. These findings confirmed the appropriateness of using this test battery as an effect measure in the RCT (Study III). There is no consensus concerning cut-off levels for acceptable absolute reliability, but a SEM (%) of 10% has been suggested\(^\text{125}\) and was used in this study together with an MDC (%) of 10% to indicate acceptable measurement error on an individual level. However, the MDC (%) was only acceptable for the 20-metre walk test and the stair-climb test, with an MDC of 0.4 and 1.2 seconds, corresponding to 10% in both tests. This means that in a clinical setting, the remaining tests should be considered inappropriate.

The present study reveals better reliability in leg extension power (ICC 0.91 and MDC 34 W) than a recent intra-rater study on hip OA patients (ICC 0.72 and MDC 43 W).\(^93\) This difference could be explained by the disparity between the included patients (pre versus post total hip replacement) or it could be a result of the standardised verbal commands in the present study or differences in test procedures. Concerning the functional tests, our results are in line with their findings.\(^93\)

Previous studies on inter-rater reliability of isometric strength measurements on healthy adults using a hand-held dynamometer have discovered that problems associated with strength of the rater can influence the results.\(^\text{126, 127}\) In contrast, we found no systematic differences between raters in the hand-held dynamometer measurements. A possible explanation is that when measuring patients with affected lower-limb strength, as after total hip replacement, the problem of adequate rater-strength might be less marked. In an inter-rater study using hand-held dynamometer performed on hip OA patients, Poulsen et al.\(^\text{128}\) found lower ICCs in hip abduction strength (0.38-0.85) and hip flexion strength (0.55) than in our study. As in the previous comparison concerning leg extension power, this difference could be caused by the sound file, a more pronounced standardisation of test procedures, or the differences between the study populations. The relative reliability of isometric strength test in the present study is comparable to findings from a pilot test of inter-rater reliability in connection with an intervention study on total hip replacement.
patients. With regard to hip abduction strength, the two studies found identical ICCs of 0.93, and with regard to hip flexion ICCs were comparable: 0.83 versus 0.88.

In summary, our reliability results are comparable to previous studies and superior on the leg extension power test. The results indicate that it is feasible to use more than one assessor when applying this test battery in THR patients at a group level as is done in intervention studies. The standardisation of verbal commands by use of a simple sound file played on a computer is considered an easy and effective method to reduce the impact from the rater’s voice and accentuation.

7.3 Effect of progressive resistance training (Study III)

7.3.1 Muscle function results
Contrary to our hypothesis, we found no additional effect of the PRT in improvements in leg extension power. This is in contrast to the previous studies on effectiveness of PRT early after THR.60, 61, 64-66 There might be various explanations for this, as discussed in the following section.

Lack of effect in exercise studies is often explained by insufficient intensity or dose of the exercises, in other words poor therapeutic validity is suggested to result in negative study findings.129 In the present study, we applied the recommended intensity, sets and frequency of the exercises,77, 81 controlled by comprehensive supervision and high training compliance. The planned progression of absolute load was achieved without exacerbating pain, as shown in Figure 4. Thus we judge the execution, intensity and frequency of the intervention to be sufficient. The applied duration of the PRT is debatable though, since there is no conclusive evidence concerning the optimal training period of PRT for elderly81 or after THR.130 Commonly, a minimum of 12 weeks of PRT are applied.82 We wanted a short training period in order to enhance patient inclusion, which was expected to be difficult because of the need for transportation to biweekly training sessions shortly after surgery. Short training duration would also improve the possibility of implementation in the clinic if successful results were obtained. Since earlier studies have shown an effect of resistance training over shorter time frames (5-8 weeks),61, 71 we considered 10 weeks to be an acceptable compromise, knowing that it would result in 8-9 weeks of actual training, depending on how early start-up was accomplished. However, in light of our results showing tendencies of effect but no convincing between-group differences, our results may have been affected by the training period being too short.
In Table 11 the relative improvements from the present study concerning muscle power and strength are compared to the two previous studies on PRT after THR.

Table 11. Strength gains during intervention period in studies on PRT after THR

<table>
<thead>
<tr>
<th>Study</th>
<th>Mikkelsen</th>
<th>Suetta$^{64-66}$</th>
<th>Husby$^{60,61}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks of PRT</td>
<td>10</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Strength measurement</td>
<td>Leg extension power + isometric</td>
<td>Isokinetic +isometric</td>
<td>1 RM test of the trained exercises</td>
</tr>
<tr>
<td>Muscle group</td>
<td>Leg extension</td>
<td>Hip abduction</td>
<td>Hip flexion</td>
</tr>
<tr>
<td>Immediate effect of PRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRT group</td>
<td>+21%*</td>
<td>+26%*</td>
<td>+18%*</td>
</tr>
<tr>
<td>Control group</td>
<td>+17%*</td>
<td>+12%*</td>
<td>4%NS</td>
</tr>
<tr>
<td>Long term effect (½ year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRT group</td>
<td>+42%</td>
<td>+32%</td>
<td>+24%</td>
</tr>
<tr>
<td>Control group</td>
<td>+27%</td>
<td>+25%</td>
<td>+11%</td>
</tr>
</tbody>
</table>

PRT: Progressive resistance training, THR: Total hip replacement, *Significant different from preoperative (p<0.05), NS Not significant different from preoperative (p>0.05), †Difference to preoperative not tested

In the present study, the strength gains are slightly smaller but comparable to those found by Suetta et al.$^{64-66}$ This is judged to be a satisfactory result of the training in light of their intervention and effect being solely on the quadriceps muscle, which is probably less influenced by surgery than the muscles surrounding the hip. Furthermore, the implementation of fast-track procedures and general improvements in surgery potentially forms a different basis for training after surgery. In their study from 2004, the length of hospital stay was dramatically longer, with 10 and 16 days in the two groups compared to 1-2 days in our study. This suggests that their control group was more immobilised, thereby making larger differences possible because of a better potential for improvements. This speculation is confirmed by the difference in strength development in the control groups of these two studies, where our CG shows greater improvements during 10 weeks after surgery than their CG during 12 weeks. When comparing to the study by Husby et al.$^{60,61}$ it should be noticed that their intervention period was only 5 weeks and the strength measurements used was 1RM of the trained exercise. This effect measure might reflect further issues than only muscle strength improvements; the patients in the IG probably improved their technique during training and not just their muscle strength. However, they report
much larger gains in hip abduction strength intermediating and in the long term compared to our study, and much less strength gains in leg press compared to our results on leg extension power.

In comparison to a recent Danish study concerning preoperative exercises, we found less improvements in leg extension power, their follow-up being 3 months after THR and all patients receiving outpatient physiotherapy post discharge (~30% compared to 21% in the IG in the present study). An explanation could be the different baseline levels: ~74 watts in their study compared to ~117 watts in our study. It seems that the samples of THR patients recruited are very different concerning leg extension power, even though both studies are randomised training studies performed in the same time period in Denmark. This difference in baseline power is surprising since we aimed at excluding the best functioning patients, which was not the case in the study by Villadsen et al.

*Effect modification by gender*

Interestingly, it seems that gender modifies the effect of PRT on leg extension power of the operated leg. As shown in Table 10, there is significant effect of the intervention among the females, whereas among males the direction of the effect is opposite, though not significant. This could be speculated to be caused by a lower power at baseline and thereby larger potential for improvements, but baseline level in leg extension power does not modify the effect of PRT (Table 10). Neither does age nor BMI modify the effect of the intervention. The literature on gender differences are divergent, with studies claiming that gender does not affect the response to resistance training and others claiming that men achieve larger responses. Our results are contrary to this, with the women showing the best response to PRT. The explanation of this finding remains unknown, but it might be explained by the hypothesis that strength adaptations in women are less dependent on hypertrophy and to a larger extent depend on neuromuscular adaptations compared to men. If this is the case, it could explain this surprising finding, since the surgical stress response results in catabolism, which might blunt hypertrophy and thereby decrease the response to PRT in men more than in women. It must be emphasised that these analysis and speculations are solely explorative and hypothesis generating.

**7.3.2 Functional performance**

The functional tests performed in Study III are comparable to those used in the study by Suetta et al. Some of the functional tests improved significantly more with PRT compared to home-based exercises: sit-to-stand performance in their study, walking speed and stair climb performance in the present study. In their study, PRT resulted in comparable but slightly larger improvements compared to our study (walking speed: 30% versus 21%, stair test: 28% versus 26% and sit-to-stand test: 30% versus
25%\textsuperscript{)}\textsuperscript{66} As mentioned before, we believe that the patient’s potential for improvement was larger in their study. This is supported by comparison of the two control groups that both received home-based rehabilitation. The functional performance in the CG in the present study improved significantly (12-20%, p<0.05), which was not the case in the previous study (-16% to +22%, p>0.05).\textsuperscript{66} The maximum walking speed improved more in our IG (21%) than in the before-mentioned study\textsuperscript{94} on preoperative exercises (14-18%), even though baseline speed was slightly slower and their follow-up period slightly longer. All together, the functional performance gains after PRT found in the present study comply well with expectations based on current literature, but the CG improved more than expected.

7.3.3 Patient reported outcome

There were no significant between-group differences on the HOOS subscales in Study III. The HOOS results indicate a rapid and substantial recovery in both groups, comparable with intervention groups in other studies.\textsuperscript{31, 94} It is surprising that this intervention, with a considerably larger amount of supervision than in the CG, did not affect the patient-reported outcome. An explanation could be that the substantial improvements in the CG make it impossible to attain significantly larger improvements by new interventions. The present study showed slightly larger improvement on the HOOS ADL scores in both groups compared to the study by Villadsen et al. on preoperative training.\textsuperscript{94} After 10 weeks the IG improved by 40 points and the CG by 37 compared to their 3-month improvement of ~30 points, with comparable baseline values.\textsuperscript{94} Ceiling effects of ≥20% at maximum scores were observed for all HOOS subscales (except sport/recreation) from the 6 month’s follow-up and forward, indicating that the suitability of the questionnaire in long-term follow-up after THR might be disputed.

7.3.4 Summary on findings in Study III

Overall, a comparison with earlier studies indicates that the IG in the present study achieved the expected gains after PRT; the surprising finding is the comparable improvements in the CG. All outcome measures improved slightly more in the IG than in the CG, indicating that there might be an effect of the intervention that did not reach statistical significance in the present study. However the differences are considered too small to be clinically meaningful in light of the rather comprehensive and expensive intervention, with 20 sessions of high intense one-to-one supervised PRT.
7.4 Limitations

7.4.1 Selection bias
We consecutively included all THR patients in Study I as part of the quality assessment in the department and with relatively high response rates. Accordingly, we assume that there is a minimum of selection bias in that study population. In Study I, the patients tended to be slightly older, more females, less healthy and less frequently received cementless prosthesis than in Study III, where informed consent was obtained (Table 6), indicating presence of selection bias in Study III. This is underlined by comparing the baseline mean HOOS ADL score in Study I (~45) to Study III (~50), implying that the patients in Study III perceived less functional limitations even though the best functioning patients were excluded. This selection bias is probably caused by the demands for participation. The patients should be willing to participate in training twice a week and attend one extra follow-up visit at the hospital. The transportation to the training was a crucial point for participation since 58 patients refused participation for that specific reason (shown in Paper III). We believe that the exclusion of the best functioning patients to some degree counteracts the typical selection bias in intervention studies, i.e. that participants are less disabled than non-participants.\textsuperscript{132, 133} However, the comparisons to Study I reveal that Study III is probably affected by some selection bias, and we assume that we had an over-representation of motivated patients. In the reliability study (II), we do not consider the selection to be crucial; thus we used convenience sampling. The samples in Study II do not deviate notably from the other studies with regard to age, gender and BMI (Table 6).

7.4.2 Blinding
In Study I, the physiotherapists performing the ADL evaluation were unblinded to intervention due to the before-after design of the study. This could cause information bias if the physiotherapists considered one intervention to be superior to the other and unknowingly evaluated that group better. This was prevented by keeping the evaluations and answers very simple and giving thorough instructions on how to evaluate the tasks. Furthermore, it was emphasised that it was unknown which rehabilitation regimen that was superior in improving independency in ADL functions.

In Study II, the rater of the second test was blinded to the first test results.

Blinding of the assessors in Study III was secured through randomising late during hospital stay and reminding the patients not to mention their group assignment, and by performing the PRT in other facilities and with other personnel than the tests.
However, blinding of the patients was impossible; thus a positive expectation could influence the outcome after PRT in a positive direction.

7.4.3 Other limitations

In both Study I and Study III multiple comparisons were made, and this induces a risk of type I error. Hence, the significant differences found in secondary outcomes should be interpreted with caution and in relation to the clinical relevance of the findings.

An overlap in inclusion period between Study I and Study III caused a procedure change concerning movement restrictions during patient inclusion in Study III. Equal distributions into the two groups in Study III were secured through block randomisation. Furthermore, it resulted in a larger burden of outcome measurement for a subsample of 20 participants in Study III. We attempted to minimise this by collecting data on the studies jointly; the double-participants attended the 4-week follow-up visit as used in Study III, this visit counted as the 3-week follow-up in Study I. We deemed this to be feasible since the double-participant group was a fairly small number of the sample in Study I, and since the timing of this follow-up visit also could vary by a week in normal practice. The HOOS questionnaire was used in both studies, and the same answer was used in both studies, with extra measurement times in Study III.

Study I

The missing answers regarding the primary outcome in the RG limited the conclusions that could be drawn concerning perceived function. The non-randomised design could affect the validity of the group comparisons. We cannot eliminate the possibility that unmeasured confounders biased the results. However it strengthens the design that baseline variables were reasonably distributed between groups and that the inclusion period was fairly short, hence minimising the influence of general developments in surgery and treatment practice. The short follow-up period limits the conclusions to the first 6 weeks of recovery. Since movement restrictions and use of assistive devices was only part of the rehabilitation within the first 6 weeks, we found that a follow-up period of this length was adequate.

Study II

It is recommended that around 50 participants are included in reliability studies.\textsuperscript{134} Hence, the sample size is considered a limitation in the present study even though calculated sample size requirements were fully met.
Besides the before-mentioned selection bias, the limitations of this study encompass risk of attention bias due to a considerable difference in the amount of supervision provided in the compared groups. To comply with the possible risk of attention bias, it would have been optimal to perform supervised placebo training in the CG, but this was not deemed feasible. However, the results do not indicate presence of attention bias since the primary outcome and the patient reported outcome was not superior in the IG. During the study period, 15% of the participants dropped out. Drop outs were distributed equally between the groups and predominantly related to major complications or emerged diseases. Results from the intention-to-treat and extended per protocol analysis on leg extension power were similar, indicating no systematic bias due to drop outs. Hence the drop outs are considered unrelated to the intervention and not affecting the internal validity of the study. In addition, two patients had to discontinue the intervention, implying that a subgroup of patients might not tolerate the PRT. However, we did include all participants in all analysis regardless of their training attendance.

### 7.5 Generalisability
The results from Study I we believe to be highly generalisable to the general population of patients with OA going through THR surgery. This is based on the consecutive enrolment of all patients at the department, without asking for participation. However, the results on the variables at 3-week follow-up with low response rates have questionable generalisability.

In Study II, we selected patients of a certain age group (55-80 years) and without musculoskeletal comorbidities, thus our results are only generalisable to that group of patients. Many patients refused to participate in the study (51%), which could further affect the generalisability if the non-participants were systematically different from participants. We do not believe the patient selection to be problematic in this case because to the reasons for non-participation were mostly practical (time issues at the specific test day), and because the study investigated reliability of the tests, no comparison between patients were made.

Selection bias seemed to be a problem in Study III, as described in section 7.4.1, and thereby the generalisability is affected. We may have included motivated patients with a positive attitude towards training. Drop outs among the weakest patients might further decrease the generalisability of the results to the most disabled group of THR patients. Patients that did not complete the study tended to be older, weaker and more were women compared to those who completed. All together, the results can presumably be generalised to motivated THR patients with an intermediate level
of perceived function, meaning that the patients with the highest level were excluded and patients with the lowest level tended to refuse participation or drop out of the study.
8. Conclusion

Study I
We found slightly slower but equal recovery on perceived function in the UG compared to the RG, but potential bias leads to inconclusive results. However, less restricted rehabilitation led to earlier return to work, more independence in functional capacity, and a substantial decrease in the use of assistive devices, while hip dislocation rates, levels of anxiety, depression and patient satisfaction were comparable to the restricted group.

Study II
The tests battery showed acceptable relative and absolute inter-rater reliability on a group level, but not on an individual level, because only tests of walking speed and stair climb performance proved acceptable absolute reliability. After THR, the 30-second sit-to-stand test is recommended over the five repetitions sit-to-stand test.

Study III
Supervised progressive resistance training 2 days/week in combination with home-based exercise 5 days/week was not superior to daily home-based exercise in improving leg extension power of the operated leg 10 weeks after THR. For some of the secondary outcomes, results were in favour of PRT but were deemed clinically insignificant. Significant improvements in muscle function, functional performance and patient-reported outcomes were achieved 10 weeks after THR, despite group assignment, except regarding hip flexion muscle strength in the CG.
9. Perspectives and future research

Most of the previous literature on outcome and rehabilitation after THR is based on patients undergoing conventional THR surgery. The results covered in this thesis underline the need for future research to establish the functional performance and muscle strength outcomes after fast-track surgery without supervised rehabilitation. This could indicate whether there is need for supervised rehabilitation and form the basis for an impairment-based approach in future rehabilitation studies. To establish the need for supervised rehabilitation, it is necessary to define what is full recovery – or acceptable recovery – after fast-track THR. This is a complex issue to address, because increases from the preoperative level do not reflect whether or not the patients are sufficiently recovered, since the preoperative level of muscle function and functional performance are affected by pain and disuse. The contralateral leg has been used as a measure for recovery, but it can hardly be considered an unaffected leg due to OA often being bilateral. Furthermore, between-limb comparisons are mainly relevant concerning muscle function, and the functional tests do seldom distinguish between legs. Comparison to healthy peers is an alternative approach and has been used previously. If patient satisfaction and patient-reported outcomes were to determine full recovery then the goals seem to be achieved for the vast majority of patients. However, there is a discrepancy between what THR patients perceive they can do physically and what they actually can do as described in the introduction. Thus, it is relevant to consider all these aspects of functional recovery in future studies.

Before this thesis there was a general consensus in the literature that high-intense resistance training would probably be a solution to overcome the documented deficits after THR since they were mainly muscle strength related. Several authors requested studies on PRT after THR. However, the results from this thesis indicate that the PRT is not as effective as expected. These findings do not claim to be exhaustive, but need to be confirmed or contradicted in future research. There might be a subgroup of patients profiting from PRT and maybe different timings and dosages could change the conclusions. Based on this thesis, it is speculated that women might benefit from PRT after THR, but this needs to be verified in future studies. Different rehabilitation strategies could also be investigated, for instance, general physical activity. The current literature is sparse but suggests that THR patients do not fully utilise their functional gains from surgery in the form of increasing their daily activity level to that of healthy controls. Maybe interventions aiming at increasing general physical activity and returning to sport rather than specific hip exercises would be beneficial. Another approach is functional task exercises, and recent studies support the effect of these interventions as shown in
Table 3. In the future, personalised rehabilitation might be a possibility if it is possible to identify subgroups of patients that benefit the most from specific intervention. There is large variation in all the physical and patient-reported outcomes used in this thesis, indicating that THR patients are heterogeneous when it comes to their health status before surgery, their gain from THR and their response to rehabilitation interventions. It seems that some recover well with use of unsupervised home-based exercises and return to an active lifestyle. It is speculated that some patients need PRT to fully recover – and this could be women – while some need functional exercises and maybe some need quite different approaches. In future training studies, the transportation to the training sessions should be considered since it was a general reason for non-participation in Study III. In an optimal design, the patients should have easy access to the training facility, and it should not require driving a car. This is specifically important early after surgery, and it could counteract some of the selection problems.

Concerning movement restrictions after THR, the optimal regimen needs to be established. This thesis indicates beneficial effects of fewer restrictions, but the evidence is still inconclusive concerning the safety in relation to risk of hip dislocation. Large scale prospective studies with complete follow-up are needed. This is challenging, since register-studies involve potential problems with the coding procedures, and in clinical studies non-response can be associated with higher dislocation risk. Thus a meticulous effort should be made to attain complete follow-up.
10. References


List of appendices

Appendix 1: Paper I


Appendix 2: Paper II


Appendix 3: Paper III


Appendix 4: List of theses from the orthopaedic research group
Appendix 4

List of theses from the orthopaedic research group
THESES FROM THE ORTHOPAEDIC RESEARCH GROUP

PhD and Doctoral Theses from the Orthopaedic Research Group, www.OrthoResearch.dk, University Hospital of Aarhus, Denmark

PhD Theses

1. In vivo and vitro stimulation of bone formation with local growth factors
   Martin Lind, January 1996
   www.OrthoResearch.dk

2. Gene delivery to articular cartilage
   Michael Ulrich-Vinther, September 2002
   www.OrthoResearch.dk

3. The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
   Ole Rahbek, October 2002
   www.OrthoResearch.dk

4. Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
   Søren Kold, January 2003
   www.OrthoResearch.dk

5. Stimulation and substitution of bone allograft around non-cemented implants
   Thomas Bo Jensen, October 2003
   www.OrthoResearch.dk

6. The influence of RGD peptide surface modification on the fixation of orthopaedic implants
   Brian Elmengaard, December 2004
   www.OrthoResearch.dk

7. Biological response to wear debris after total hip arthroplasty using different bearing materials
   Marianne Nygaard, June 2005
   www.OrthoResearch.dk

8. DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups
   Mogens Berg Laursen, November 2005
   www.OrthoResearch.dk

9. Studies based on the Danish Hip Arthroplasty Registry
   Alma B. Pedersen, 2006
   www.OrthoResearch.dk

10. Reaming procedure and migration of the uncemented acetabular component in total hip replacement
    Thomas Baad-Hansen, February 2007
    www.OrthoResearch.dk

11. On the longevity of cemented hip prosthesis and the influence on implant design
    Mette Ørskov Sjoland, April 2007
    www.OrthoResearch.dk

12. Combination of TGF-β1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo
    Anders Lamberg, June 2007
    www.OrthoResearch.dk
13. Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration  
   Inger Mechlenburg, August 2007  
   *Acta Orthopaedica (Suppl 329) 2008;79*

14. Rehabilitation of patients aged over 65 years after total hip replacement - based on patients’ health status  
   Britta Hørdam, February 2008  
   www.OrthoResearch.dk

15. Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty  
   Kristian Larsen, May 2008  
   www.OrthoResearch.dk

16. Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants  
   Mette Krintel Petersen, June 2008  
   www.OrthoResearch.dk

17. CoCrMo alloy, *in vitro* and *in vivo* studies  
   Stig Storgaard Jakobsen, June 2008  
   www.OrthoResearch.dk

18. Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs  
   Jørgen Baas, July 2008  
   *Acta Orthopaedica (Suppl 330) 2008;79*

19. The Influence of Local Bisphosphonate Treatment on Implant Fixation  
   Thomas Vestergaard Jakobsen, December 2008  
   www.OrthoResearch.dk

20. Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults  
   Anders Troelsen, March 2009  
   *Acta Orthopaedica (Suppl 332) 2009;80*

   Maiken Stilling, June 2009  
   *Acta Orthopaedica (Suppl 337) 2009;80*

   Thomas H.L. Jensen, September 2009  
   www.OrthoResearch.dk

23. Osteoclastic bone resorption in chronic osteomyelitis  
   Kirill Gromov, November 2009  
   www.OrthoResearch.dk

24. Use of medications and the risk of revision after primary total hip arthroplasty  
   Theis Thillemann, December 2009  
   www.OrthoResearch.dk

25. Different fixation methods in anterior cruciate ligament reconstruction  
   Ole Gade Sørensen, February 2010  
   www.OrthoResearch.dk
26. Postoperative pain relief after total hip and knee replacement; prospective randomized studies evaluating two different peri- and postoperative regimes
   Karen V. Andersen, June 2010
   www.OrthoResearch.dk

27. A comparison of two types of osteosynthesis for distal radius fractures using validated Danish outcome measures
   Jesper O. Schønnemann, September 2010
   www.OrthoResearch.dk

28. Optimizing the cementation of femoral component in hip arthroplasty
   Juozas Petruskevicius, September 2010
   www.OrthoResearch.dk

29. The influence of parathyroid hormone treatment on implant fixation
   Henrik Daugaard, December 2010
   www.OrthoResearch.dk

30. Strontium in the bone-implant interface
    Marianne Toft Vestermark, January 2011
    www.OrthoResearch.dk

31. The applicability of metallic gold as orthopaedic implant surfaces – experimental animal studies
    Kasra Zainali, April 2011
    www.OrthoResearch.dk

32. Gene transfer for bone healing using immobilized freeze-dried adeno-associated viral vectors
    Mette Juul Koefoed, June 2011
    www.OrthoResearch.dk

33. Mobile or fixed bearing articulation in TKA? A randomized evaluation of gait analysis, implant migration, and bone mineral density
    Michael Tjørnild, December 2011
    www.OrthoResearch.dk

34. Hip resurfacing arthroplasty. Failures and complications investigated by a meta-analysis of the existing literature, and clinically by microdialysis, laser doppler flowmetry, RSA, DXA and MRI
    Nina Dyrberg Lorenzen, March 2012
    www.OrthoResearch.dk

35. Manipulation of the mevalonate pathway in the bone-implant interface
    Mette Sørensen, September 2012
    www.OrthoResearch.dk

36. Bone allograft and implant fixation tested under influence of bio-burden reduction, periosteal augmentation and topical antibiotics
    Jeppe Barckman, January 2013
    www.OrthoResearch.dk

37. Sternal healing characteristics. Animal and clinical experimental investigation
    Rikke Vestergaard, March 2013
    www.OrthoResearch.dk

38. Assessment of factors influencing the surgical outcome of periacetabular osteotomy for treatment of hip dysplasia in adults
    Charlotte Hartig-Andreasen, June 2013
    www.OrthoResearch.dk
39. Stem cells derived from adipose tissue and umbilical cord blood for cartilage tissue engineering in scaffold cultures
   Samir Munir, December 2013
   www.OrthoResearch.dk

40. Flexor tendon adhesions – a mouse model of flexor tendon injury and repair
   Sys Hasslun Svensson, 2014
   www.OrthoResearch.dk

41. The association between obesity and the effect of total knee – and hip arthroplasty
   Anette Liljensøe, 2014
   www.OrthoResearch.dk

**Doctoral Theses**

1. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
   Kjeld Søballe, 1993
   *Acta Orthop Scand (Suppl 255) 1993;54*

2. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
   Martin Lind, October 1998
   *Acta Orthop Scand (Suppl 283) 1998;69*

3. Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
   Søren Overgaard, 2000
   *Acta Orthop Scand (Suppl 297) 2000;71*

   Steffen Jacobsen, December 2006
   *Acta Orthopaedica (Suppl 324) 2006;77*

5. Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
   Michael Ulrich-Vinther, March 2007
   *Acta Orthopaedica (Suppl 325) 2007;78*

6. Assessment of adult hip dysplasia and the outcome of surgical treatment
   Anders Troelsen, February 2012
   www.OrthoResearch.dk