Joakim Mælashaug Ordahl

Knee Osteoarthritis and Pain Fluctuations

A single subject design study

Master thesis in Sports Physiotherapy
Department of Sports Medicine
Norwegian School of Sport Sciences, 2015

Abstract

Background: Osteoarthritis is one of the most common chronic pain disorders, pain is the dominant symptom, and exercise is one of the key elements in the conservative management. The nature of pain in osteoarthritis patients has earlier been considered relatively stable. However, this view of pain is challenged in the literature.

Objective: To evaluate pain fluctuations over time among middle-aged patients with mild to moderate knee osteoarthritis undergoing a 14-week exercise intervention.

Material and Methods: This study was part of a randomized controlled trial (Oiestad et al., 2013) investigating the efficacy of strength and aerobic exercise in middle-aged patients with knee osteoarthritis. Eleven knee osteoarthritis patients were followed in this single subject design study. During a 16 week period (1 week baseline + 14 week intervention + 1 week post intervention) patients were regularly (assessments daily during the baseline phase and the post intervention phase, weekly during the intervention phase) assessed with the pain subscale of the Knee Osteoarthritis Outcome score (KOOS) and the Numeric Rating Scale (NRS) for pain.

Results: The mean fluctuation (difference between the highest score and the lowest) during the intervention phase was 28 points measured with the KOOS pain and 7 points measured with the NRS for pain. Comparing with the post intervention phase, pain fluctuation measured with the KOOS pain was higher during the intervention phase for all subjects except one. Measured with the NRS for pain, all subjects had higher pain fluctuation during the intervention phase compared to the post intervention phase. Comparing the post intervention phase with the baseline phase, all but two subjects had higher pain fluctuations at the baseline phase compared to the post intervention phase measured with the KOOS pain. Measured with the NRS for pain, all but one subject had higher pain fluctuations at the baseline phase compared to the post intervention phase.

Conclusion: This study showed that overall, according to a cutoff of ten points for the KOOS pain and two points for the NRS for pain patients with knee osteoarthritis reported clinically meaningful (MCID) pain fluctuations during a 14-week intervention period. Pain fluctuations varied substantially among the eleven subjects. In general, pain fluctuated less at the post intervention phase compared to the baseline phase and the intervention phase. The results from this study add to the literature documenting pain fluctuations in patients with knee osteoarthritis.

Table of contents

Acknowledgements

First and foremost I would like to thank my fantastic supervisor May Arna Risberg for guiding me through this master's thesis. I am very thankful for all the time you spent helping me. Your enthusiasm and knowledge for science is admiring.

Margreth Grotle, thank you for great feedbacks and sharing of your great knowledge in the area of pain science.

Britt Elin Øiestad and Kristin Bølstad, thank you for helping me with the data collection. You were always so positive and helpful.

Thanks to my girlfriend for proofreading and supporting me through the process.

I would also like to thank all the patients who participated in this study. Thank you for answering all the questionnaires.

Joakim Mælashaug Ordahl

May 2015, Oslo

1. Introduction

Osteoarthritis is one of the most prevalent chronic pain disorders (Lawrence et al., 1998), and the knee joint is commonly affected (Dieppe & Lohmander, 2005). The most dominant symptom associated with osteoarthritis is pain (Bijlsma et al., 2011). Pain in osteoarthritis patients has earlier been considered relatively stable, and changes of the pain experience has been associated with activity and rest (Allen et al., 2009). However, this view of pain in osteoarthritis is challenged in the literature.

Osteoarthritis has been diagnosed primarily with plain radiography (X-rays) and clinical examination for many decades (Cibere, 2006), however radiographic findings are an imprecise marker to what extend a knee is painful (Bedson & Croft, 2008). Hence, there is likely that several mechanisms are influencing the pain experience in people with knee osteoarthritis (Maly, Costigan, & Olney, 2008). Why there is a poor correlation between disease severity and the level of pain and disability reported lack knowledge (Hunter, McDougall, & Keefe, 2009).

Historically, cartilage damage was believed to be the main reason for the pain experience in people with osteoarthritis. Today there is a perception that several other factors are influencing the pain experience. Other type of joint damage such as effusion, synovial thickening and bone attrition are among factors related (Maly et al., 2008). Imaging studies have shown the presence of inflammation, synovitis and bone marrow lesions which may mediate pain (Sofat, Ejindu, & Kiely, 2011). Among other factors with significant impact on pain experience in this patient population are psychological factors (Maly et al., 2008). Psychological factors may modulate pain signals, hence influencing the pain perception. Moreover, peripheral sensitization and especially central sensitization have been proposed as two of the underlying pain mechanisms in osteoarthritis (Lluch, Nijs, Torres-Cueco, & Lopez, 2013).

Exercise is a usual treatment to improve function and reduce pain for patients with osteoarthritis (Nelson, Allen, Golightly, Goode, & Jordan, 2013). Different kinds such as aerobic, strengthening, endurance and flexibility exercises are common, both land-based and water-based. According to the Osteoarthritis Research Society International

there is good evidence for the use of the exercises mentioned for people with osteoarthritis of the knee (McAlindon et al., 2014).

Despite the big amount of research done in the area of osteoarthritis there are still lacking knowledge why osteoarthritis are painful (Sofat et al., 2011) and why exercise work as treatment (Sofat et al., 2011; Beckwee, Vaes, Cnudde, Swinnen, & Bautmans, 2013). Pain is the main reason patients with osteoarthritis seek medical help, and more knowledge to gain a deeper understanding of pain pathways could improve management of the disease (Sofat et al., 2011).

Traditionally, pain has been assessed in clinical trials by asking patients about their current pain at baseline and again after intervention (Williams et al., 2004). This may however lead to wrong conclusions, given that pain can fluctuate widely from one week to the next. Assessing patients pain level over a period of time could potentially be more representative than one assessment at baseline and one after intervention. To our knowledge no study has previously investigated daily and weekly pain fluctuations in a Norwegian population with osteoarthritis. Earlier studies investigating pain fluctuations have been looking at pain fluctuations in a population not receiving an exercise intervention. Literature documenting pain fluctuation in patients with osteoarthritis is growing, however more research is needed (Allen et al., 2009).

The purpose of this study was therefore to evaluate pain fluctuations among knee osteoarthritis patients undergoing an exercise intervention. This master's thesis was part of a randomized controlled trial (Oiestad et al., 2013), an ongoing investigation of the efficacy of strength and aerobic exercise in middle-aged patients with knee osteoarthritis. There are two intervention groups and one control group included in the ongoing study. One group has tailored strength exercises, a second group perform cycling (aerobic exercises), and a third control group do as they usually do (but are asked to not start physiotherapy treatment or exercises the first four months of the study period).

The recruitment of subjects to the randomized controlled trial (Oiestad et al., 2013) started march 2013 and is still ongoing today. A total of 207 subjects are planned to be included. For this master's thesis; 22 consecutively included patients in the randomized

controlled trial from August 2014 were tested for eligibility for this master's thesis single subject design project.

2. Objective

2.1 Overall purpose

The purpose of this study was to evaluate pain fluctuations over time among middle-aged patients with mild to moderate knee osteoarthritis undergoing a 14-week exercise intervention.

2.2 Main research question

How does pain fluctuate in middle-aged patients with mild to moderate knee osteoarthritis undergoing a 14-week exercise intervention?

2.3 Research questions

- Are pain fluctuations at baseline, during the 14-weeks intervention and at post intervention different from each other?
- Are baseline and post intervention KOOS pain scores different from the KOOS pain scores these same individuals reported in the ongoing randomized controlled trial (Oiestad et al., 2013)?

2.4 Hypotheses

- Pain fluctuations is expected to be 10 points or more for the KOOS pain and 2 points or more for the NRS for pain during the 14-week intervention
- Pain fluctuations are decreased post intervention compared to baseline fluctuations and fluctuations during the 14-week intervention
- Baseline and post intervention KOOS pain scores reported for the included subjects in this study are different from the KOOS pain scores they reported in the randomized controlled trial (Oiestad et al., 2013)

3. Theoretical background

3.1 Definition and classification

The term osteoarthritis describes pathological changes in a synovial joint (Dieppe & Lohmander, 2005). Joint failure results from an imbalance between mechanical stresses and catabolic processes acting on the joint, and the ability of the joint tissue to withstand and repair the damage (Nuki, 1999). When the dynamic equilibrium between the breakdown and repair of joint tissue is overwhelmed, it is when osteoarthritis occurs. Rather than being viewed as a single disease or process, osteoarthritis can be viewed as the clinical and pathological outcome of a range of disorders characterized by structural and symptomatic failure of one or more synovial joints (Nuki, 1999).

Usually osteoarthritis is classified as either primary (idiopathic) or secondary (Nuki, 1999). When there is no obvious single predisposing cause osteoarthritis is classified as primary, while when it follows some clearly defined predisposing pathologies it is classified as secondary. Osteoarthritis classified as primary is most common (Flugsrud et al., 2010), and 70-80% of Norwegians who receive a total hip or knee replacement are diagnosed with primary osteoarthritis (Nasjonalt kompetansesenter for leddproteser, 2009). Most common causes for secondary are injury, infection, tumor, avascular necrosis, and the childhood hip disorders Legg-Calvé-Perthes syndrome, dysplasia and epifysiolysis (Flugsrud et al., 2010).

3.2 Diagnosis

The diagnosis of osteoarthritis should in clinical practice be made on the basis of your history and physical examination (Hunter et al., 2009). The role of radiography is to confirm the clinical findings and rule out other conditions. American College of Rheumatology have developed clinical criteria for the diagnosis and classification for symptomatic osteoarthritis of the knee (Altman et al., 1986).

Table 1: *The American College of Rheumatology clinical classification criteria for symptomatic osteoarthritis of the knee (Altman et al., 1986).*

One must have articular knee pain for most days of the prior month, in addition to at least 3 of the following: 1. Crepitus on active joint motion 2. Morning stiffness <30 minutes duration 3. Age >50 years 4. Bony enlargement on the knee on examination 5. Bony tenderness of the knee on examination 6. No palpable warmth

This way of classifying knee osteoarthritis gave a sensitivity of 95% and specificity of 69% (Altman et al., 1986). In The American College of Rheumatology original publication several different ways of classifying osteoarthritis were proposed, giving different sensitivity and specificity. They also proposed classification criteria based on clinical examination, laboratory tests or radiographs either in combination or alone (Altman et al., 1986). It was believed that no single classification criteria could satisfy all circumstances to which the criteria for osteoarthritis of the knee would be applied, hence separate sets of classification criteria were developed for use in different circumstances.

The American College of Rheumatology criteria for knee osteoarthritis have been revised several times after first being proposed in 1986 (Wu et al., 2005). Especially the age criteria are often used differently since osteoarthritis could occur earlier than the age of 50 years. In a study by Wu et al. (2005) revising these criteria, the inclusion criteria for age were 40 years or older.

Kellgren and Lawrence were the first to carry out large-scale epidemiological studies of osteoarthritis in the 1950s. They diagnosed osteoarthritis based on x-rays (KELLGREN & LAWRENCE, 1957), diagnostic criteria that are still widely used (Felson, Niu, Guermazi, Sack, & Aliabadi, 2011).

Table 2: *Kellgren and Lawrence classification system (KELLGREN & LAWRENCE, 1957).*

Grade	Description
0	No changes
1	Doubtful narrowing of joint space and possible osteophytic lipping
2	Definite osteophytes and possible narrowing of joint space
3	Moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis, and possible deformity of bone ends
4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Unfortunately, neither Kellgren and Lawrence or users of their scale were consistent in how they described each of the grades in the classification (Felson et al., 2011). Especially grade 2, which usually define whether radiologic osteoarthritis is present, have been used inconsistently.

3.3 Epidemiology

Osteoarthritis is a very common disease (van Saase, van Romunde, Cats, Vandenbroucke, & Valkenburg, 1989), and one of the most common chronic musculoskeletal diseases (Pereira et al., 2011). It is the most common form of arthritis (Vos et al., 2012), the economic burden of osteoarthritis is enormous (Gupta, Hawker, Laporte, Croxford, & Coyte, 2005), and the number of people with osteoarthritis is increasing. Prevalence, incidence, and risk of developing the disease depend on how data are collected and how osteoarthritis is diagnosed. In a Norwegian study called "Ullernsaker-undersøkelsen" where a sample of the general population between 24-76 years of age were included, every eighth participant reported they had the diagnosis diagnosed by a physician (Grotle, Hagen, Natvig, Dahl, & Kvien, 2008). A Dutch study found the prevalence of radiologic hip osteoarthritis to be 10-20% in the age group 70-80 years (van Saase et al., 1989). Moreover, they found the prevalence of radiologic knee osteoarthritis to be 20-40% and hand osteoarthritis to be 60-80%. The American population has a 45% lifetime risk of developing symptomatic knee osteoarthritis according to a cohort study (Murphy et al., 2008). In another study also investigating the American population, the estimated lifetime risk for developing knee osteoarthritis was 14% (Losina et al., 2013). Estimated median age which knee osteoarthritis was diagnosed was 55 years. The authors (Losina et al., 2013) explain the difference in numbers with different ways of collecting data. Furthermore, projected lifetime risk was estimated from different ages, from 25 years in the study by Losina et al. (2013) and

from 45 years in the study by Murphy et al. (2008). In addition, the population was different in the two studies.

The most common joints affected by osteoarthritis are hands, knees, hips, and spine (Dieppe & Lohmander, 2005). A single joint could be affected, however commonly several joints are involved. In 2013 4937 persons had a total knee replacement in Norway, and 4010 of those were due to osteoarthritis (Nasjonalt kompetansesenter for leddproteser, 2014). While osteoarthritis is very common in the knee, it is even more prevalent in the hands (Hunter et al., 2009). Especially the distal interphalangeal joints (DIP), the proximal interphalangeal joints (PIP), and the carpometacarpal joints (CMC).

3.4 Pathophysiology

Osteoarthritis are as mentioned a disease that affects synovial joints, and all joints are possibly affected (Dieppe & Lohmander, 2005). Characterizations of the disease are progressive cartilage loss, subchondral bone remodeling, osteophyte formation and synovial inflammation (see figure 1) (Hunter, 2011). When one component of the joint is affected, the other components of the joint will be affected secondary (Flugsrud et al., 2010).

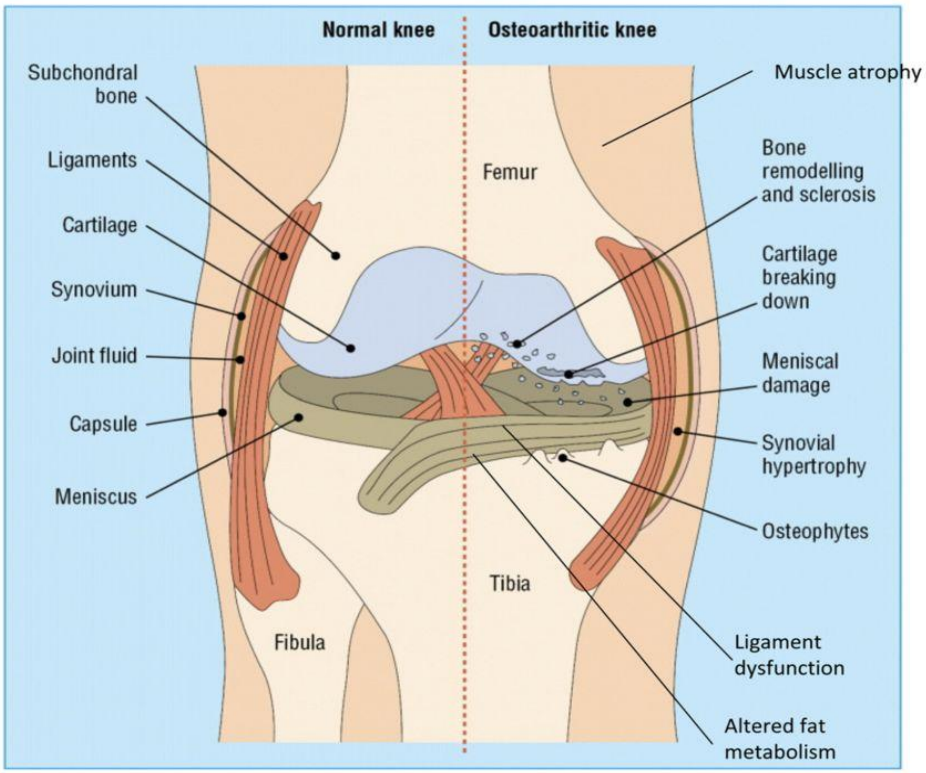


Figure 1: *Characteristics of an osteoarthritic knee. Reproduced with permission from Hunter (2011).*

We can divide osteoarthritis into three stages. The early stage of osteoarthritis is marked by morphological changes in the otherwise-smooth and well-lubricated articular cartilage that covers the joint surfaces (Sovani & Grogan, 2013). In the mid stage increased cell death and homeostatic imbalance leads to increased catabolic mediator activity and degradation of the extracellular matrix. Progression of the mid stage will finally end in cartilage destruction. In the late stage of osteoarthritis a hallmark is the formation of cell clusters containing cells that indicate a hopeless attempt of tissue regeneration (Sovani & Grogan, 2013).

Traditionally, loss of cartilage has been the main focus of osteoarthritis (Altman et al., 1986). However, because osteoarthritis involves all tissue of the synovial joint the emphasis on the loss of cartilage is misguided (Brandt, Dieppe, & Radin, 2008). Osteoarthritis could be viewed as failed repair of damage that has been caused by excessive mechanical stress on joint tissue.

Inflammation is present in an osteoarthritic joint to a variable extent, however how much the inflammation contributes to joint damage is questionable (Felson, 2013). Likely, the basis of the joint damage in osteoarthritis is caused by mechanically induced injury according to Felson (2013). Evidence shows that injury to the joint can lead to secondary inflammation. Also, treatment to correct mechanics has been superior to treatment to correct inflammation. Thus, inflammation in osteoarthritis is most likely a consequence of pathomechanics (Felson, 2013). Joint injury could cause joint damage without involvement from the inflammation, however the inflammation can accelerate or magnify the injury that is produced by pathomechanics. While inflammation is likely contributing to further destruction of the osteoarthritic joint, abnormal mechanics is the basis of osteoarthritis claims Felson (2013). On the other hand according to Berenbaum (2013) recent findings arguments in favor of osteoarthritis as an inflammatory disease. Low-grade inflammation induced by the metabolic syndrome, innate immunity and inflammaging are among these arguments.

The aetiology of osteoarthritis is perhaps best understood as a result of excessive mechanical stress applied in the context of systemic susceptibility (Hunter, 2011). Nevertheless, the pathophysiology of osteoarthritis is still not fully understood (Buckwalter & Martin, 2006).

3.5 Risk factors

Risk factors for osteoarthritis could be divided into modifiable and non-modifiable risk factors. We can possibly influence the modifiable risk factors in clinical practice, and it is only by understanding the impact of the disease and the modifiable risk factors that we will truly be able to target public health preventions appropriately (Johnson & Hunter, 2014).

3.5.1 Non-modifiable risk factors

Age is a risk factor for developing osteoarthritis, and the prevalence of the disease is increasing with increasing age (Chaganti & Lane, 2011). It is thought that aging have an adverse effect on the ability of the joint to protect itself from biomechanical stress.

Large database studies have shown that different ethnicities have different prevalence of osteoarthritis (Chaganti & Lane, 2011). Difference in sex is also observed, the prevalence among woman are higher than among men. Furthermore, genetics seems to play a role. Twins studies have indicated that as much as 40-60% of all incidences of idiopathic osteoarthritis are due to genetics (Valdes & Spector, 2009).

3.5.2 Modifiable risk factors

The two best documented risk factors for osteoarthritis are obesity and joint injury (Johnson & Hunter, 2014). The risk factors show some variation depending of localization. Osteoarthritis of the knee are associated with obesity, but also osteoarthritis of the hip and hand show association with obesity even though this association is weaker than for the knee (Magliano, 2008). The association between hand osteoarthritis and obesity indicates that biomechanics alone does not fully explain the reason. Hormonal or nutritional factors are suggested as the reason why obesity is linked to the risk of osteoarthritis, without any conclusive documentation to support this theory (Grundy et al., 2005). In addition the increased load obesity cause is thought to be contributing. During gait, each additional kilogram of body mass increases the comprehensive load over the knee by roughly four kilogram (Messier, Gutekunst, Davis, & DeVita, 2005).

Hence, the question whether mechanical or systemic factors are most important for developing osteoarthritis has been raised (Cicuttini & Wluka, 2014). Han et al. (2013)

found no association between metabolic syndrome and knee osteoarthritis in their study. Contrary, Monira et al. (2014) did find an association between metabolic syndrome and knee osteoarthritis. In the study by Visser et al. (2014) mechanical stress were found to be the most important risk factor for knee osteoarthritis, whereas systemic factors were found to be the most important risk factor for hand osteoarthritis.

Injuries, especially of the knee are predisposing to osteoarthritis (Johnson & Hunter, 2014). The numbers in the literature vary, however there are consensus that the risk of osteoarthritis increases after traumatic knee injuries and the surgery that often follows these injuries. Sports activities itself does not seem to increase the risk of osteoarthritis, as long as the intensity are at a moderate to low level (Hunter & Eckstein, 2009). In contrast, elite sports participation seems to be associated with increased risk of osteoarthritis. The nature of the sport is very important to the degree of risk though, and it is not clear whether participation in elite sport in the absence of injury is harmful.

Physical activity seem to be safe for the knee joint, however very high levels and high force is a potential risk of developing osteoarthritis (Ratzlaff, Koehoorn, Cibere, & Kopec, 2012). Joint tissue are sensitive to their mechanical environment, and moderate mechanical loading maintains the integrity of articular cartilage, while disuse and overuse can result in cartilage degradation (Sun, 2010). Repetitive joint use such as kneeling and squatting are increasing the risk of osteoarthritis (Johnson & Hunter, 2014), and studies have found individuals whose occupations require this have twice the risk of developing knee osteoarthritis compared with occupations without these physical demands (Messier et al., 2009).

Other potential risk factor for knee osteoarthritis are weakness of quadriceps femoris and knee malalignment (Johnson & Hunter, 2014). Moreover, anatomical abnormalities are associated especially with hip osteoarthritis (Chaganti & Lane, 2011).

3.6 Pain and symptoms

Pain is the dominant symptom of osteoarthritis, and the main reason patients seek medical help (Bijlsma et al., 2011). Loss of movement and function is another major problem for osteoarthritis patients, and are closely associated to the level of pain (Hutchings et al., 2007). This may limit patients in activities of daily living such as stair

climbing, walking and doing household chores. Muscle atrophy is seen secondary to inactivity (Stemberger & Kerschan-Schindl, 2013). Stiffness is also a common symptom, however this stiffness generally resolves in minutes unlike the prolonged stiffness caused by rheumatoid arthritis (Bijlsma et al., 2011). The stiffness is experienced in the morning, after a period of inactivity, or in the evening, and lasts usually less than 30 minutes.

Joint enlargement results from joint effusion, bony swelling, or both, and may be seen in patients with osteoarthritis (Bijlsma et al., 2011). Crepitus, a sensation of crunching or crackling, is commonly felt on passive or active movement of an osteoarthritic joint. If loose bodies or fragments of cartilage get into the joint space, the joint can lock. Moreover, an osteoarthritic joint could be instable, buckling or giving way (Hunter et al., 2009). The rest of this chapter will be focusing on the most dominant symptom in osteoarthritis patients, which is pain.

3.6.1 Pain

Pain is defined by the International Association of the study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey & Bogduk, 1994). According to this definition, cognitive and emotional aspects are always involved in a pain experience. Pain might vary in intensity (mild, moderate, or severe), quality (sharp, burning, or dull), duration (transient, intermittent, or persistent), and referral (superficial or deep, localized or diffuse) (Woolf, 2004). Mechanisms behind pain could be several including nociception, peripheral sensitization, phenotypic switches, central sensitization, ectopic excitability, structural reorganization, and decreased inhibition.

Pain is often classified according to the duration: acute pain and chronic or persistent pain (Woolf, 2004). Acute pain contributes to survival by protecting us from injury or promoting healing when injury has occurred. Chronic or persistent pain is defined by the International Association for the study of Pain as pain that persists past the healing phase following an injury (IASP, 1986). The first type of pain is adaptive, while the latter is clearly maladaptive (Woolf, 2004). To determine the end of the healing phase is difficult, however the common clinical definition is instead a fixed time of persistent pain following its initial onset (Apkarian, Baliki, & Geha, 2009). Usually this time is set

to three or six months, although it is difficult to classify one time period for all different pain conditions.

3.6.2 How pain manifests in patients with osteoarthritis

Typically osteoarthritis presents as joint pain which is exacerbated by activity and relieved by rest (Hunter et al., 2009). The most prominent symptom in patients with osteoarthritis is pain, which fluctuates over time and across different activities (Dimitroulas, Duarte, Behura, Kitas, & Raphael, 2014). In periods osteoarthritis patients might experience acute flare-up of pain, for example after a high load of activity (Hunter et al., 2009). In later stages of osteoarthritis, pain can be experienced at rest and during the night. The pain is often described as deep aching, and not well localized. In the past osteoarthritis pain has been considered relatively stable other than changes with activity and rest (Allen et al., 2009). However, the literature showing pain fluctuations in patients with osteoarthritis is growing.

In a focus group study (Hawker et al., 2008) patients described two distinct types of pain as their disease progressed. The first pain was described as dull, aching, throbbing, which became more constant over time. The second pain was described as more intense, often unpredictable, and emotionally draining. Furthermore, patients described their pain as worsening over time which was expected. They also distinguished their experience of pain depending of the progression of the disease. In the early stage of osteoarthritis pain was characterized by predictable sharp pain, usually brought on by a trigger which could be an activity such as sport. Eventually the pain limited high impact activities such as skiing, but had relatively little other impact (Hawker et al., 2008).

In the mid stage of osteoarthritis, the patients described the predictable pain as increasing and the pain become more constant (Hawker et al., 2008). The pain started to affect activities of daily living such as walking and climbing stairs. In the advanced stages of osteoarthritis a constant dull and aching pain with short episodes of often unpredictable intense pain was described. The time from the insidious onset of pain until the advanced stage with a constant dull and aching pain were usually several years (Hawker et al., 2008).

Allen et al. (2009) examined within-day pain patterns in patients with osteoarthritis. They found pain patterns to differ substantially across individuals. Furthermore, patients reported a significant range of pain scores within a day, with a mean range of about 35 points between maximum and minimum ratings on a scale from 0-100. Pain was measured on one weekday and one weekend day using a handheld computer, with ratings beginning immediately after waking then approximately every two hours following. A sliding visual analog scale with a hidden coding of 0-100 was used to rate the pain. Bellamy et al. (2002) also found pain to change within a day in patients with hand osteoarthritis. Participants self rated pain on a 10 cm horizontal visual analogue scales six times a day for ten consecutive days. Pain was found to change systematically throughout the day, showing circadian rhythmicity.

The Longitudinal Examination of Arthritis Pain study examined pain variations on a weekly basis in adults diagnosed with hip or knee osteoarthritis (Hutchings et al., 2007). Participants reported pain levels and other health outcome measures through weekly telephone interview for twelve weeks. Weekly pain ratings on an 11-point scale (0=no pain, 10=extreme pain) indicated within-week pain fluctuation of about two points. In addition, decreases in the patient reported pain were associated with improvements in daily activities and decreases in work absenteeism, sleep interference, and healthcare resource use. These results were showing the importance of the small changes in pain levels (Hutchings et al., 2007).

Pain was described as changing month by month, day by day, and by the time of the day in a qualitative study of patients with hip and knee osteoarthritis (Gooberman-Hill et al., 2007). Patients took part in six focus groups describing and discussing their experience of joint pain in the context of the questionnaires Hip Disability and Osteoarthritis Outcome score and Knee Injury and Osteoarthritis Outcome score. The focus groups were audio recorded and transcribed. Data were analyzed resulting in the identification of key categories. Patients characterized their pain in these four key categories: “pain is intermittent and variable”, “pain elsewhere in the body influences the experience of joint pain”, “pain is inextricable from function”, and “adaptation and avoidance strategies modify the experience of pain”. Although pain has been shown to fluctuate on a daily (Allen et al., 2009; Bellamy, Sothern, Campbell, & Buchanan, 2002), weekly (Hutchings et al., 2007) and monthly (Gooberman-Hill et al., 2007) basis, the amount of

research done in this area is relatively scarce (Allen et al., 2009). Thus the knowledge about pain fluctuations in patients with osteoarthritis is still limited.

3.6.3 Biopsychosocial model of osteoarthritis pain

Historically, cartilage damage was believed to be the main reason for the pain experienced in people with osteoarthritis (Sofat et al., 2011). Hence, nociceptive pain was considered the primary type of pain in osteoarthritis (Dimitroulas et al., 2014). Although cartilage damage still is assumed to be an important factor in the disease progress of osteoarthritis, there is increased knowledge regarding the fact that several other factors are influencing the pain experience. Both inflammatory and neuropathic pain has been shown to be contributing to the pain experience.

At present, there is research clearly indicating that there is a discordance between radiographic knee osteoarthritis and the pain experienced (Bedson & Croft, 2008), although the discordance is less with more severe stages of radiographic disease (Neogi, 2013). Magnetic resonance imaging seem to predict clinical pain better than x-rays (Staud, 2011). Nevertheless, radiographic imaging cannot be used solely to predict osteoarthritis pain (Cibere, 2006). This is adding to the understanding that the pain experienced with osteoarthritis might not only be due to biomedical reasons. Why there is disconnect between disease severity in form of joint degeneration and the level of pain experienced, is not fully understood (Hunter et al., 2009).

Thus a shift from the traditional biomedical view of the pain experience in osteoarthritis towards a biopshycosocial is needed (Hunt, Birmingham, Skarakis-Doyle, & Vandervoort, 2008). The biopsychosocial model also includes the biomedical part, but in addition psychological factors and social factors are taken into account. How people cope with the osteoarthritis pain may vary, hence psychosocial factors might possibly affect how patients experience the osteoarthritis pain.

The evidence for the importance of psychosocial variables in explaining osteoarthritis pain is emerging (Somers, Keefe, Godiwala, & Hoyler, 2009). Especially cognitive variables such as pain catastrophizing and self-efficacy show consistent links to pain. Social support and pain communication are also important considerations in understanding the pain experience (Hunter, Guermazi, Roemer, Zhang, & Neogi, 2013).

Other psychosocial factors like environment and employment play a substantial role in determining the level of disability and pain (Hunt et al., 2008). All this add to the perception that osteoarthritis should be viewed in a biopsychosocial framework, and addressing all the dimensions is of importance when pain is to be explained and managed.

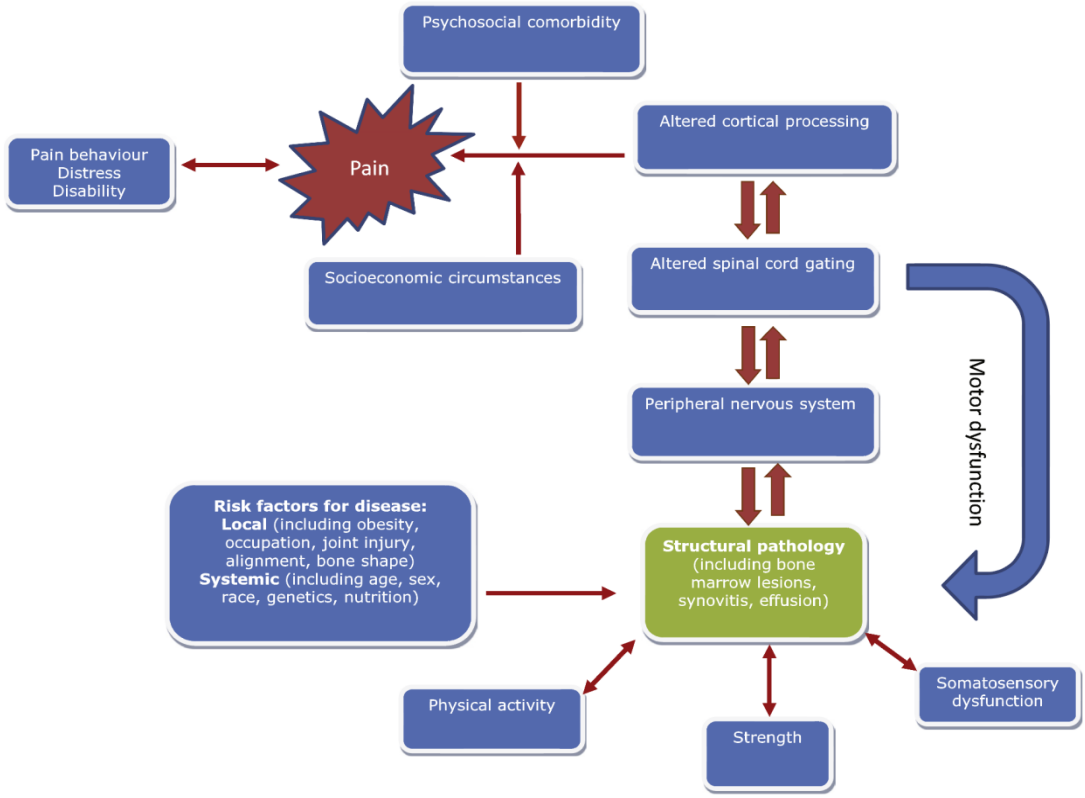


Figure 2: *Biopsychosocial model highlighting the relation of structural pathology to the pain experience. The model shows that there are many variables behind the pain experience. Reproduced with permission from Hunter et al. (2013).*

3.6.4 Potential pain mechanisms in osteoarthritis

Despite pain being the primary symptom and main cause of disability, much remains to be clarified about the potential mechanisms behind osteoarthritis pain (Mease, Hanna, Frakes, & Altman, 2011). The following paragraphs give a summary of potential mechanisms underlying the pain experience in patients with osteoarthritis.

Nociception

Activation of specialized sensory neurons called nociceptors lead to the sensation of pain (Murphy, Phillips, Williams, & Clauw, 2012). Usually, activation of nociceptors

only occurs in the presence of a noxious stimulus. Although abnormal cartilage damage is a key hallmark of osteoarthritis, cartilage is avascular and hence aneural (Mease et al., 2011). Nociceptors are accordingly not found in cartilage, and damaged articular cartilage is therefore not capable of directly generating pain in osteoarthritis (Felson, 2005). However, there are several other structures in the joint with nociceptors (see paragraphs below).

Worth noticing is that according to a review of Sofat et al. (2011) previous literature describing cartilage entirely avascular and aneural has recently been challenged, suggesting modifications occur during osteoarthritis disease. A study by Suri et al. (2007) demonstrated that a substantial number of fine nerve terminals may be present in osteoarthritic cartilage. Studies have demonstrated a relation of cartilage damage to pain, however the likely mechanisms for symptom genesis are through secondary mechanisms that comes along with the cartilage damage according to Hunter et al. (2013). Other structures in the synovial joint are innervated by nociceptors, and these are the likely source for the pain experienced in these studies claims the author.

Periarticular bone changes associated with osteoarthritis are among these mentioned other structures in the synovial joint, which are potential sources for the pain experienced (Hunter et al., 2013). Changes include progressive increase in subchondral plate thickness, alterations in the architecture of subchondral trabecular bone, formation of new bone at the joint margins (osteophytes), development of subchondral bone cysts and advancement of the tidemark associated with vascular invasion of the calcified cartilage.

Bone marrow lesions are the osseous change with most supportive evidence for a role in symptom genesis (Hunter et al., 2013). According to Hunter et al. (2013) there is some conflicting data, however the balance of data would support a strong relation between bone marrow lesions and pain in osteoarthritis. Other bone related causes of pain are periostitis associated with osteophyte formation, subchondral microfractures, bone attrition and bone angina due to decreased blood flow and elevated intraosseous pressure.

Synovitis and effusion are also often present in an osteoarthritic joint, and are correlated to pain (Hunter et al., 2013). Included in the synovial reaction in osteoarthritis is synovial hyperplasia, fibrosis thickening of synovial capsule, and activated synoviocytes (Roach, Aigner, Soder, Haag, & Welkerling, 2007). The presence or absence of synovitis may even be an independent predictor of pain experienced in osteoarthritis (Bonnet & Walsh, 2005). However, the exact contribution of inflammation to pain in osteoarthritis is uncertain and may vary from time to time and from patient to patient. It is today unclear whether inflammation is a feature of all patients with osteoarthritis at some stage of their disease process, or whether synovitis itself defines one subgroup of the osteoarthritis disease.

Another potential source of pain in osteoarthritis is the outer rim of the meniscus, which is innervated (Ashraf et al., 2011). Meniscal damage is a common feature of knee osteoarthritis, however the clinical relevance are unclear. In a study by Bhattacharrya et al. (2003) a meniscal tear was found in 76% of asymptomatic patients with a mean age of 65 years using MRI, whereas 91% of patients with symptomatic knee osteoarthritis had a tear. Thus the clinical relevance of meniscal tears in elderly patients with knee osteoarthritis may be limited (Hunter et al., 2013). Other tissues such as periostium, periarticular ligaments, and perarticular muscles spasm are richly innervated and are all potential sources of nociception in osteoarthritis (Hunter et al., 2009).

Peripheral sensitization

When tissue injury occurs, it leads to an inflammatory response with release of inflammatory mediators (Staud, 2011). Inflammation in the joint trigger a cascade of events leading to increased sensitivity of nociceptive neurons, which we call peripheral sensitization (Mease et al., 2011). The threshold of nociceptive neurons are lowered, hence nociceptors respond to non-noxious stimuli (allodynia) and the response to noxious stimuli is exaggerated (hyperalgesia). Gentle stimuli which normally do not activate them, might be sufficient to excite the nociceptors (Schaible, Schmelz, & Tegeder, 2006).

As the cartilage in osteoarthritis is destroyed, inflammatory mediators are released (Haringman, Ludikhuize, & Tak, 2004). Inflammation triggers as mentioned a cascade of events driven by the inflammatory mediators, leading to enhanced cartilage turnover

and matrix degradation (Dimitroulas et al., 2014). There are many degenerative structural changes within the joint in osteoarthritis other than cartilage damage, which can trigger inflammation. Especially bone marrow lesion, synovitis and effusion have been recognized (Hunter et al., 2013). When the disease progresses, more of these mediators accumulate in the joint, hereby triggering a self-perpetuating cycle of pain generation (Hunter et al., 2009).

One proposed hypotheses suggests osteoarthritis as an autoinflammatory disease (Konttinen, Sillat, Barreto, Ainola, & Nordstrom, 2012). The articular cartilage can produce substances that are able to cause pain and secondary inflammation, and this mechanism suggests that osteoarthritis could be considered as an autoinflammatory disease.

In addition to the sensory neurons nociceptors, so-called silent nociceptors exist (Schaible et al., 2006). These neurons are not activated as long as the tissue is normal, however when the tissue is inflamed these silent nociceptors are sensitized and they start to respond. The awakening of the silent nociceptors is assumed to contribute to intensifying joint pain sensation in arthritis (Hunter et al., 2009).

Central sensitization

Central nociceptive transmission in the dorsal horn can also be sensitized like the peripheral nociceptors (Hunter et al., 2009). The threshold for activation falls and responses to sequent inputs are amplified (Latremoliere & Woolf, 2009). When central sensitization is present pain could arise spontaneously, be elicited by normally innocuous stimuli (allodynia), have prolonged and exaggerated response to noxious stimuli (hyperalgesia), spread beyond the site of injury (secondary hyperalgesia), and even be widespread according to Latremoliere & Woolf (2009). It should be known that there are different opinions in the literature around the phenomenon central sensitization, and to what extent this phenomenon is the mechanism behind pain seen in the clinic (Hansson, 2014).

It is believed that peripheral sensitization play an important role in the development and maintenance of central sensitization (Mease et al., 2011). Repeated input from peripheral nociceptors modulate nociceptors in the spinal cord leading to increased

synaptic excitability and decreased firing threshold (Scholz & Woolf, 2002). Central sensitization has both spinal and supraspinal components (Schaible, 2012). Depression of spinal inhibitory mechanisms are also contributing to pain experience (Woolf & Salter, 2000). When the inhibitory mechanisms are not working properly, the pain experience is amplified (see figure 3). Another phenomenon termed windup are a result of abnormal repetitive stimulation of a peripheral nociceptors, which also contributes to pain intensifying (Dimitroulas et al., 2014).

3.6.5 Pain assessment

Numerous assessment tools have been developed for assessing level and quality of pain, and its impact on function (Turk & Melzack, 2011). Having a valid and reliable assessment of pain is essential for both clinical trials and effective pain management. Location, intensity and the frequency of pain are the dimensions of pain most often measured. The nature of pain however, makes objective measurement impossible. Hence, subjective assessment of pain in form of questionnaires, rating scales, and pain drawings is the common way of assessing pain.

Each assessment tool has its own strength and weaknesses (Hawker, Mian, Kendzerska, & French, 2011). Visual Analog Scale and Numeric Rating Scale (NRS) are generic unidimensional single-item scales providing estimates of patients self-reported level of pain intensity. Positive for these two assessment tools are that they are easy to administer, complete, and score. However, they are not providing a comprehensive evaluation of pain in patients with rheumatic disease (Hawker et al., 2011).

To meet the complexity of pain and to assess the multiple dimensions of acute and chronic pain, multidimensional questionnaires like The McGill Pain Questionnaire and The Chronic Pain Grade Scale have been developed (Hawker et al., 2011). These questionnaires contain questions to not only describe the quantity of pain, but also the quality. The Short Form-36 Bodily Pain Scale is another multidimensional questionnaire, which evaluates pain in a context of the overall health status. These multidimensional questionnaires are however, not as easy to administer, complete, and score as the unidimensional questionnaires (Hawker et al., 2011).

More disease specific questionnaires have been developed to even better measure the pain experienced. For osteoarthritis the Knee Injury and Osteoarthritis Outcome Score (KOOS) has been developed as an osteoarthritic-specific pain measure and is even joint specific (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). Western and Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) (Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988) and Measure of Intermittent and Constant Osteoarthritis Pain (Hawker et al., 2011) are also two disease specific questionnaires. Due to the variability and complexity of pain, and the variability in purpose, content, administration burden, and evidence to support each measurement method, no pain measure can be recommended for use in all situations (Hawker et al., 2011).

Studies including patients with osteoarthritis have found that health outcomes and the course of disease progression are related to a patient's self-efficacy (Felson et al., 2000; Brekke, Hjortdahl, & Kvien, 2003). Perceived self-efficacy is defined by Bandura (1986) as " Peoples' judgment of their capabilities to organize and execute courses of action required to attain designated types of performance" . It is concerned not with the skill one has, but measures a changeable psychological aspect of pain (Lorig, Chastain, Ung, Shoor, & Holman, 1989). Arthritis Self-Efficacy Scale (Lorig et al., 1989) is a questionnaire developed to measure this dimension.

3.7 Treatment

There is no known cure for osteoarthritis (Stemberger & Kerschan-Schindl, 2013). Management of osteoarthritis is in international recommendations often divided into three main categories: non-pharmacological, pharmacological and surgical (Zhang et al., 2010). Because till now osteoarthritis is an irreversible condition, the overall treatment goal is to reduce pain and to improve function while minimizing the potentially harmful side effects of medications and potentially reduce progression of the disease (Zhang et al., 2007). Improving health-related quality of life is also of essential interest (Stemberger & Kerschan-Schindl, 2013). The treatment should be individualized keeping in mind the patients demands, but the treatment options are diverse (Stemberger & Kerschan-Schindl, 2013). See figure 3 for a summary of treatment options for osteoarthritis. The emphasis of this theory chapter is non-pharmacological treatment of knee osteoarthritis.

3.7.1 Non-pharmacological treatment

Exercise

Exercise is recommended as treatment for osteoarthritis thoroughly in international guidelines (McAlindon et al., 2014; Hochberg et al., 2012; Fernandes et al., 2013). A Cochrane review (Fransen et al., 2015) investigating exercise for osteoarthritis of the knee revealed a beneficial effect with a standardized mean difference of 0.49 for pain and 0.52 for physical function. These effect sizes are in line with effect sizes reported for non-steroidal and anti-inflammatory drugs. The authors conclude that high-quality evidence indicate that land-based therapeutic exercise provides short term benefit in terms of reduced knee pain and improved physical function among people with knee osteoarthritis (Fransen et al., 2015). This conclusion is in accordance with an overview of systematic reviews in patients with knee osteoarthritis (Jamtvedt et al., 2008), which found high quality evidence for exercises having small to moderate effect in this patient group.

Included in recommendations are exercises to improve flexibility, strength and endurance, although there is conflicting evidence for mixed exercise programs being more effective than focused programs (Fernandes et al., 2013). One type of exercise has not been shown to be superior to another. According to a systematic review (Juhl, Christensen, Roos, Zhang, & Lund, 2014) optimal exercise programs for osteoarthritis should have one aim, and focusing on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. A review by Bennel et al. (2013) investigating the role of muscle in the genesis and management of knee osteoarthritis concludes that exercise to improve lower limb strength and especially the quadriceps muscle is a key component in the management. The form of exercise may be supervised group classes, as individual treatment with a physiotherapist, or unsupervised at home (Stemberger & Kerschan-Schindl, 2013). All three treatment forms mentioned achieve significant treatment benefits, however the number of directly supervised exercise sessions influences treatment effect sizes (Fransen & McConnell, 2008). For best results, the program should be supervised and carried out three times a week according to Juhl et al. (2014).

There are need for more documentation regarding optimal exercise intensity and frequency (Oiestad et al., 2013). At present time we know too little about dose-response

relationship in exercise interventions on patients with osteoarthritis (Wang et al., 2012). Adherence to exercise is another important factor to the efficacy, and Wang et al. (2012) showed a possible association between high adherence to exercise and improved pain and function in knee.

Despite the overwhelming evidence for the effectiveness of exercise for osteoarthritis of the knee, underlying mechanisms of these beneficial exercise-induced effects are still scarcely understood (Beckwee et al., 2013). In a review by Beckwee et al. (2013) the authors identified theories that are proposed in the scientific literature to explain the beneficial effects of exercise on osteoarthritis of the knee. They were able to identify five main categories of components that are proposed to potentially explain the effectiveness of exercise: neuromuscular components, peri-articular components, intra-articular components, general fitness and health components, and psychosocial components.

In the neuromuscular components category, the proposed underlying mechanisms for the beneficial effect of exercise are mainly focused on the decrease of the mechanical focal peak loading of the cartilage due to the impact of exercise on these components (Beckwee et al., 2013). Mentioned neuromuscular components are muscle strength, proprioception and motor learning, energy absorbing capacity and stability. However it should be mentioned that in misaligned and lax or unstable osteoarthritis knees, high quadriceps strength is a significant risk factor for radiographic progression of osteoarthritis according to Sharma et al. (2003).

Exercise is suggested to have a positive effect on periarticular components such as connective tissue and bone. Neither rationale, scientific evidence or through which pathway exercise has an effect on these components are clear (Beckwee et al., 2013). Among intra-articular components that exercise is proposed to have a beneficial effect on are cartilage, inflammation, and joint fluid.

When it comes to the general fitness and health components it is not well described how exercise has effect on osteoarthritis of the knee via these components, other than exercise is good for fitness and health in general (Beckwee et al., 2013). In the last category psychosocial components, authors (O'Reilly, Muir, & Doherty, 1999; Rogind

et al., 1998) have suggested that exercise may influence symptoms through an enhancement of general well-being. Increase of self-efficacy, decrease of depression and placebo effects are other psychosocial components suggested to be effected of exercise (Beckwee et al., 2013).

Aquatic exercise has also shown to be beneficial for knee osteoarthritis in short term, but no long term effects have been documented (Bartels et al., 2007). The effect of water minimizes joint load, hence aquatic exercises seems particularly useful in the initial phase of exercising. However, the number of studies investigating aquatic exercise for knee osteoarthritis is low and the level of evidence on the existing studies is poor. A Cochrane review (Bartels et al., 2007) found only four studies meeting the criteria of inclusion for the review, and only one study was acceptable for analysis of knee osteoarthritis alone. Effect sizes of hip and knee osteoarthritis was not possible to separate in the other studies.

In summary, exercise should in general be recommended to patients suffering from knee osteoarthritis (Stemberger & Kerschan-Schindl, 2013). Whether exercise is a cost-effective intervention is still an open question (Hagen et al., 2012).

Weight reduction

Weight loss is especially recommended for overweight patients with knee osteoarthritis (Stemberger & Kerschan-Schindl, 2013). When we know that obesity is one of the biggest risk factors for osteoarthritis (Johnson & Hunter, 2014), it is easy to understand that weight reduction is beneficial as treatment for this patient group. One major reason for this is the reduced joint load (Bliddal, Leeds, & Christensen, 2014). Messier et al. (2005) found that for every kilogram of bodyweight lost, a fourfold reduction in the load exerted on the knee per step during daily activities is achieved. Taken into consideration thousands of steps taken every day, a reduction of this magnitude appear to be clinically meaningful (Messier et al., 2005).

Weight loss can relieve symptoms, improve function, increase quality of life, and in addition be preventive of osteoarthritis (Bliddal et al., 2014). The combination of exercise with weight loss appears to be more effective than either intervention alone for obese patients with knee osteoarthritis (Messier et al., 2004).

Education and self-management

It is a general recognition that appropriate information and education are essential in prompting adequate self-management in chronic diseases (Fernandes et al., 2013). According to a systematic review of recommendations and guidelines for the management of osteoarthritis 12 out of 15 guidelines had moderate to strong recommendations for self-management programs and education (Nelson, Allen, Golightly, Goode, & Jordan, 2014). A self-management program are recommended to include education about osteoarthritis, regular contact to promote self-care, joint protection strategies, evaluation of ability to perform activities of daily living, psychosocial interventions, and individualized treatment plans. Somewhat contrary, a Cochrane review found low to moderate evidence that self-management programs result in no or small benefits in patients with osteoarthritis (Kroon et al., 2014). According to the review self-management programs do not result in more positive and active engagement in life compared with usual care. Although the review concludes that self-management skills, pain, osteoarthritis symptoms and function may improve, the apparent benefits are small and unlikely to be of clinical importance according to the authors (Kroon et al., 2014).

Assistive devices

There is a general lack of agreement among guidelines regarding patellar taping, knee braces, medial and lateral heel wedges, and appropriate footwear and/or insoles for patients with knee osteoarthritis (Nelson et al., 2014). Walking aids and other assistive devices to improve activities of daily living are generally recommended. According to OARSI guidelines (McAlindon et al., 2014) biomechanical interventions as directed by an appropriate specialist, are recommended.

Physical modalities

Thermal modalities are recommended for knee osteoarthritis (Nelson et al., 2014), while there are uncertainty regarding the effect of transcutaneous electrical nerve stimulation (TENS) and ultrasound (McAlindon et al., 2014). Electrotherapy or neuromuscular electrical stimulation does not have appropriate documentation to be recommended.

3.7.2 Pharmacological treatment

We are lacking pharmacological treatment decelerating or reversing the cartilage degeneration in osteoarthritis, hence pharmacological treatment aims to reduce symptoms (Zhang et al., 2007). According to a review of guidelines acetaminophen/paracetamol should be used as first-line pharmacological management of osteoarthritis, while second line agents should include topical agents and oral NSAIDs (Nelson et al., 2014). Intra-articular corticosteroids are recommended for knee osteoarthritis, however there are insufficient evidence currently existing to provide a general recommendation regarding intra-articular hyaluronans.

3.7.3 Surgical treatment

Surgical treatment may be preventive or as part of symptom treatment when osteoarthritis has become severe (Flugsrud et al., 2010). When conservative treatment fails, surgical treatment such as joint replacement are considered (Singh, Dohm, & Borkhoff, 2013). Joint replacement is recommended for appropriate patients with knee osteoarthritis, normally at the end stages of the disease (Nelson et al., 2014). Total knee joint replacement and total hip joint replacement are associated with significant improvement in pain, function, and quality of life and are universally recommended in guidelines (Rhon, 2008). Joint replacement surgery is generally accepted as reliable and appropriate surgical procedure to restore function and to improve pain and quality of life when other treatments fail. At the end stage of knee and hip osteoarthritis this type of management achieves by far the most significant treatment effects. On the other hand arthroscopy with debridement is not recommended (Nelson et al., 2014).

3.7.4 Summary

First line treatment of osteoarthritis should contain information, advice and self-help (Lohmander & Roos, 2007). Included in these recommendations are education about weight loss, exercise, lifestyle alterations, simple analgesics and topical agents (see figure 3). Exercise and weight management are key elements in the conservative treatment of osteoarthritis. Pharmacological management and other non-surgical interventions such as orthoses could also be considered. If these treatment options are not sufficient, surgical treatment with joint replacement could then be considered

(Hunter & Felson, 2006). Individualizing the treatment to the patients demands is of importance and should be a certainty (Stemberger & Kerschan-Schindl, 2013).

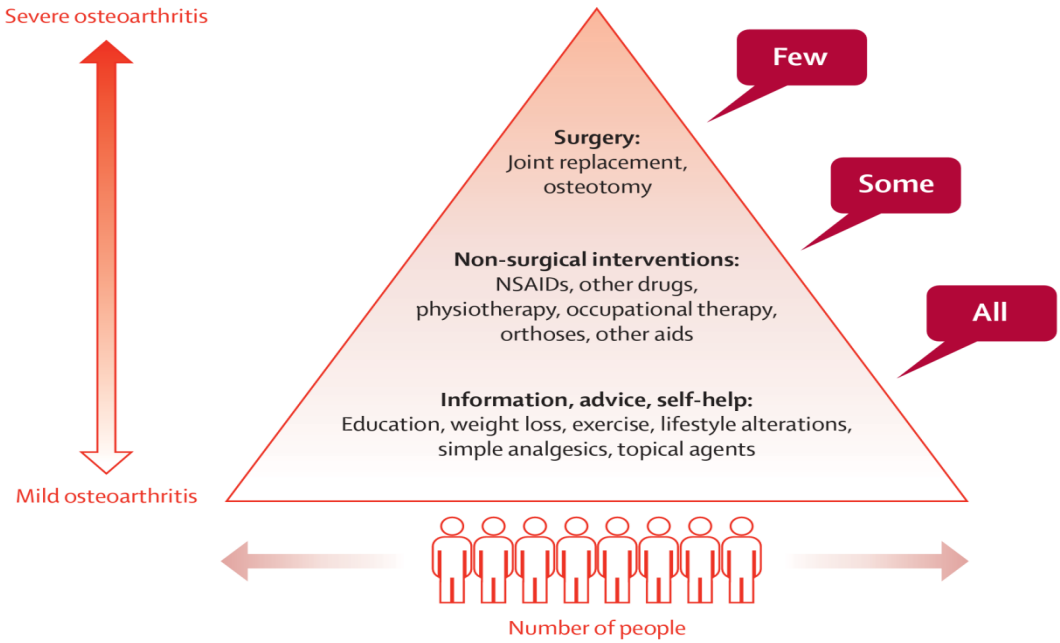


Figure 3: *Overview of treatment options for osteoarthritis depicting the number of people that need each treatment. Reproduced with permission from Lohmader & Roos (2007).*

4. Methods

This chapter will describe the study process and the assessment methods that were used.

4.1 Design

This master's thesis was a single subject design, also referred to as single system design, small-N design or idiographic research design (Ottenbacher & York, 1984). Single subject designs are an alternative to group designs, and may provide concrete data to validate existing theories as well as formulating new ones (Backman, Harris, Chisholm, & Monette, 1997). The term single subject refers to the treatment of the data and not to the number of participants in the study (Carter, Lubinsky, & Domholdt, 2011). The data from each research participant are analyzed separately and not as a group. The single subject design focus on individuals makes the research method ideally suited to document clinical change on an individual basis (Ottenbacher & York, 1984). By choosing single subject design we could therefore obtain information from the individual patient.

Single subject designs are characterized by extended periods of measurements through repeated measurements both in the baseline phase, the intervention phase, and the post intervention phase (Carter et al., 2011). Generally at least three measurements are recommended at any phase during the research, including the baseline phase. We had in our study seven assessments at the baseline phase, 14 assessments during the intervention phase, and seven assessments at the post intervention phase. The continuous assessments through the different phases (baseline, intervention, and post intervention phase) give information that can be used to monitor patient changes (linear trends and cyclic patterns) as well as progression during an intervention phase (Ottenbacher & York, 1984). Another characteristic of single subject designs are the lack of a control group (Engel & Schutt, 2005). The subject serves as their own control, as the repeated baseline measurements establish the pattern of scores that we expect the intervention to change.

Patients already participating in a randomized controlled trial (Oiestad et al., 2013) were followed over a 16 week period as part of this study. They were asked to answer questionnaires regularly throughout this period. At baseline of this 16 week period,

patients were interviewed daily by telephone for one week. They were afterwards contacted weekly during the 14 week intervention period (two weeks introduction + twelve weeks intervention). After intervention was completed in the randomized controlled trial, patients were again contacted daily for one week making it a total of 16 weeks (1 week baseline assessment + 14 week intervention assessment + 1 week post intervention assessment) (see figure 4).

4.2 Subjects

Subjects already participating in the randomized controlled trial (Oiestad et al., 2013) were recruited to this study. The recruitment process started 1st of August 2014 and was finished on the 31st of December 2014. From August 2014 the consecutively included patients in the randomized controlled trial were evaluated for eligibility in this master's thesis.

Table 3: *Inclusion and exclusion criteria in the randomized controlled trial (Oiestad et al., 2013).*

Inclusion	**Exclusion**
• Woman and men aged 45-65 years • Clinical knee osteoarthritis according to the American College of Rheumatology Clinical Criteria (Altman et al., 1986) • Kellgren and Lawrence (KL) radiographic osteoarthritis grade 2 and 3 (mild to moderate radiographic osteoarthritis)	• Severe knee osteoarthritis according to the KL classification (grade 4) • Other known major musculoskeletal impairments in the lower extremities or the back or prostheses in any joint of the lower extremities • Known serious coronary heart disease or cancer • Body mass index > 35 • Schedule for surgery in any joint • Known mental or psychological diseases • Known drug abuse • Persons who already perform sports related moderate physical activity more than two times a week • Contraindications for MRI • Not speaking Norwegian language

Only patients randomized to an intervention group in the ongoing randomized controlled trial (Oiestad et al., 2013) were included in this study. Subjects included from August 1st, 2014 until December 31st in the ongoing randomized controlled trial were asked to participate. This study planned to recruit 20 patients. The idea was to get 10 patients from each intervention group (cycling and strength exercises). Unfortunately the recruitment process was slower than expected. Since this was not an effect study, no power calculation was made as basis for the number of patients.

From August 2014, a total number of 22 patients in the randomized controlled trail (Oiestad et al., 2013) were tested for eligibility. 14 patients met the criteria for inclusion in this study, and all but one subject accepted participation. One subject (subject 6) withdrew from participation after being recruited due to difficulty understanding the questions in the questionnaires. Due to cortisone use, one subject (subject 12) was put on hold in the randomized controlled trail. Hence this subject was also excluded from this study.

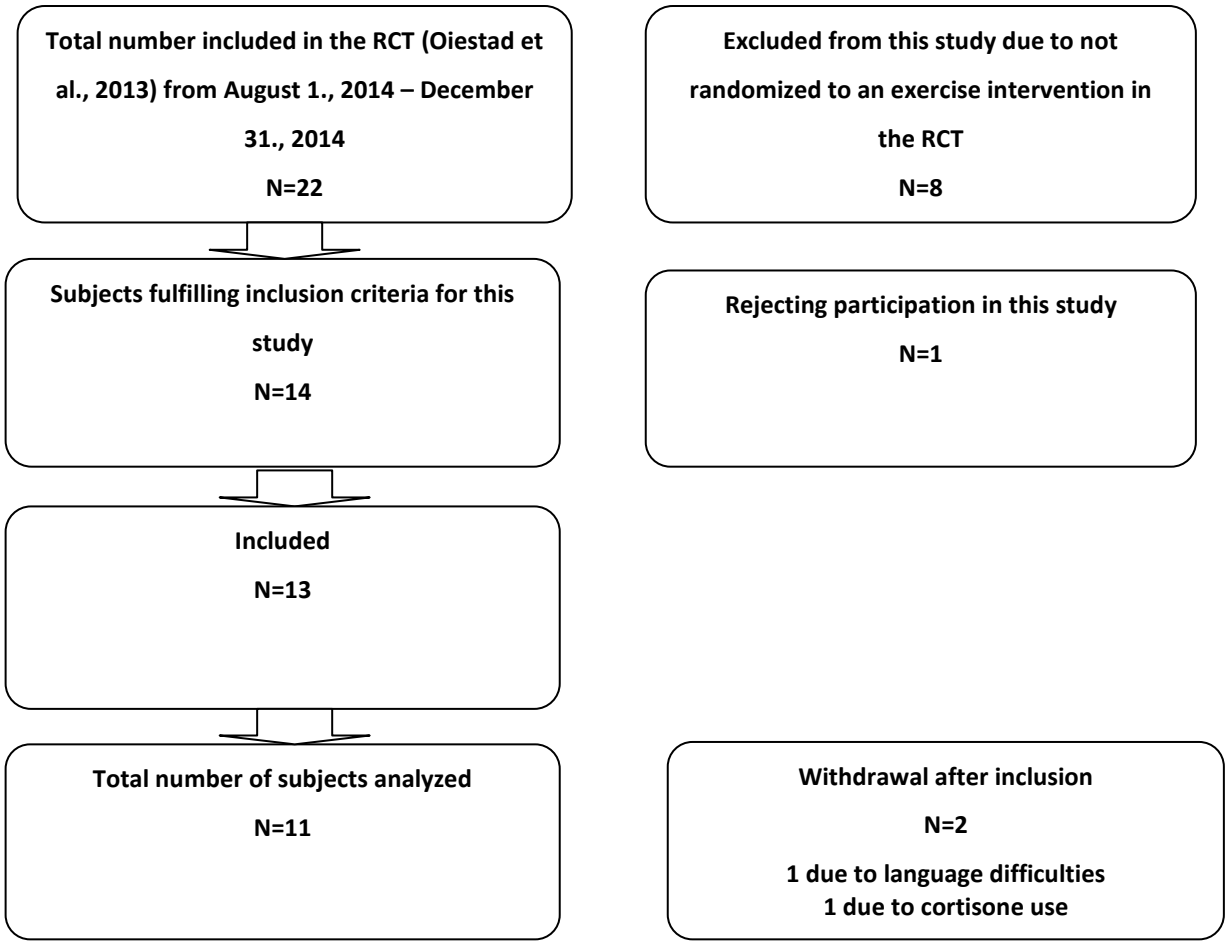


Figure 4: *Flowchart showing the recruitment process in this study.*

Due to slow inclusion in the main study (Oiestad et al., 2013) the authors decided to expand the inclusion criteria for age. From October 10th 2014, the inclusion criteria for age were set to 40-70 years. Hence, the inclusion criteria for this study also changed accordingly.

4.3 Data collection

Subjects already randomized to an intervention group in the ongoing study (Oiestad et al., 2013) were contacted either by telephone or face to face when they went through baseline assessments in the ongoing study. They were asked to participate in this study, which implied to answer additional questionnaires either by telephone interview or by email. Subjects who agreed to participate in this study were asked to answer the same additional questionnaire over a period of 16 weeks. Patients answering additional questionnaires by telephone interview did not have a copy of the additional questionnaires in front of them. The additional questionnaires were answered daily for seven days after baseline assessment in the ongoing study. During the intervention period in the ongoing study the additional questionnaires were answered weekly. When the intervention was completed in the ongoing study, patients again answered the additional questionnaires daily for seven days. Ten patients answered the additional questionnaires through telephone interview, while one patient answered by email.

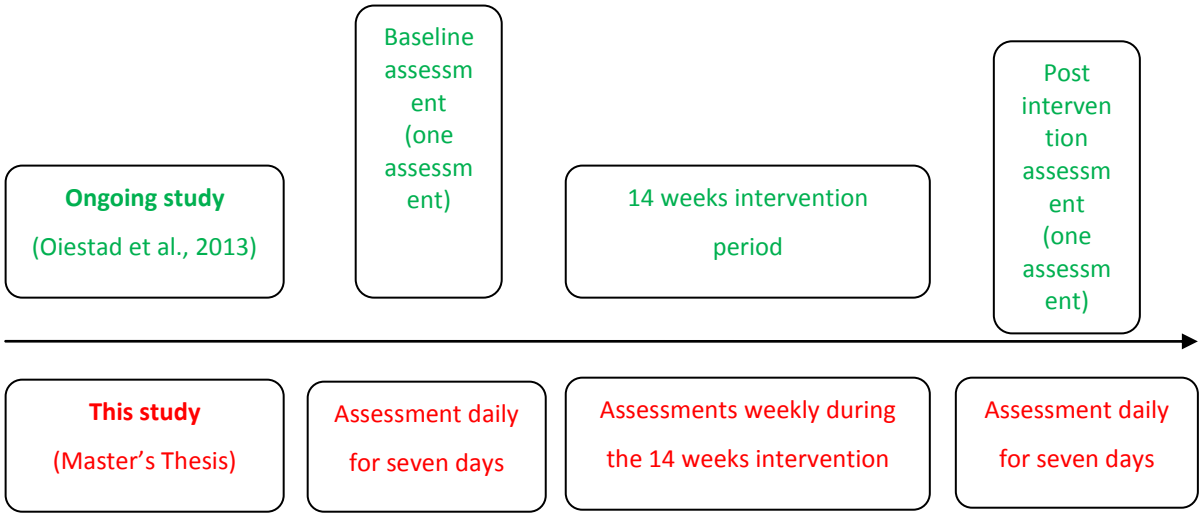


Figure 5: *Flowchart comparing the assessment process in the randomized controlled trial (Oiestad et al., 2013) and this study.*

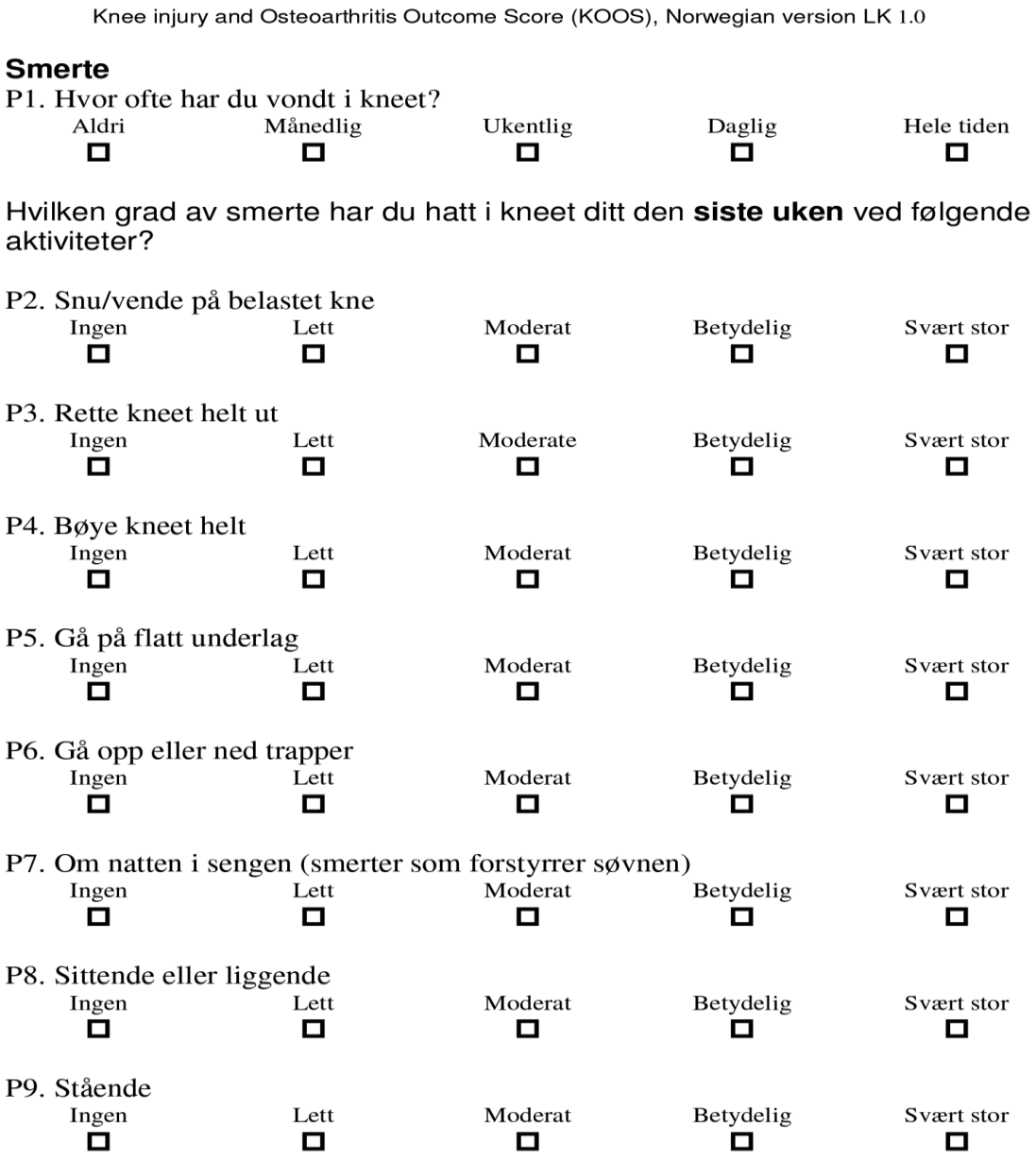
All the eleven included subjects completed assessments in both the randomized controlled trial and this study.

4.4 Assessments

In this study the assessments were the pain part of the KOOS and three questions on the NRS for pain. Background information (see table 4) and baseline KOOS scores for the other subscales (function, ADL, Sport/rec, QOL. See table 5) for the included subjects were obtained from the randomized controlled trial (Oiestad et al., 2013). The KOOS is self-administered and contains five outcomes, including pain (Roos et al., 1998). It was constructed on the basis of a literature review, an expert panel, and a pilot study. The KOOS was developed as an extension of WOMAC (Roos & Lohmander, 2003). Questions from WOMAC were included to ensure content validity for the older population with osteoarthritis. The pain section of the KOOS measure pain intensity related to activities, and includes nine questions about pain in different situations where participants are asked to rate their pain on a 5-point scale. The first question include response options "never", "monthly", "weekly", "daily" and "always". The last eight questions contain the response options "none", "mild", "moderate", "severe", and "extreme". Each response option is given a score from 0-4. The mean score is divided by four and this score is subtracted from 100 giving a final score (see www.koos.nu for details). 100 points indicates no problems and 0 indicates extreme problems. Approximately ten minutes are required to complete the full questionnaire and it can be administered by mail or in the clinic (Roos et al., 1998). Hence, the KOOS cause minimal trouble for patients and researchers and impose minimal bias.

The KOOS was developed for assessing outcome in subjects with anterior cruciate ligament injury, meniscus injury, and cartilage damage or osteoarthritis associated with knee injury, and has been proved to be a measure of sufficient reliability, validity, and responsiveness for surgery and physical therapy after reconstruction of the anterior cruciate ligament (Roos et al., 1998). Minimal clinical importance difference (MCID) has not been formally assessed for the KOOS (Roos & Lohmander, 2003). In a study conducted by Ehrich et al. (2000), ten points was found clinically relevant for osteoarthritis patients using the WOMAC pain. Since the KOOS contains the questions from the WOMAC, the ten points cutoff for clinically relevant change could also be utilized with the KOOS (Roos & Lohmander, 2003). A Swedish version of KOOS has been validated, and the clinimetric properties were found to be comparable to the American version of the KOOS (Roos, Roos, Ekdahl, & Lohmander, 1998) . The Norwegian version of the KOOS was developed on the basis of the Swedish version due

to the similarity in language and culture between the two neighbor countries. In a study validating the French version of the KOOS, minimal detectable change (MDC) was found to be 13,4 points for the pain subscale (Ornetti et al., 2008).



Knee injury and Osteoarthritis Outcome Score (KOOS), Norwegian version LK 1.0

Smerte

P1. Hvor ofte har du vondt i kneet?

Aldri	Månedlig	Ukentlig	Daglig	Hele tiden
☐	☐	☐	☐	☐

Hvilken grad av smerte har du hatt i kneet ditt den **siste uken** ved følgende aktiviteter?

P2. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P3. Rette kneet helt ut

Ingen	Lett	Moderate	Betydelig	Svært stor
☐	☐	☐	☐	☐

P4. Bøye kneet helt

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P5. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P6. Gå opp eller ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P7. Om natten i sengen (smerter som forstyrrer søvnen)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P8. Sittende eller liggende

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P9. Stående

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Figure 6: *The Norwegian version of KOOS, the pain section that was used in this study.*

The NRS for pain is an 11-point scale where participants rate their pain from 0 representing “no pain” and 10 representing “worst pain imaginable” (Hawker et al., 2011). It can be administered verbally or in written form for self-completion (Jensen, Karoly, & Braver, 1986). The time needed to complete the questionnaire is less than one

minute and NRS is easy to administer and score. Thus the burden for patients and researchers is minimal (Hawker et al., 2011). The pain NRS has been proven to be a valid and reliable scale to measure pain intensity. A reduction of approximately two points has been found to represent a clinically important difference (MCID) (Farrar, Young, Jr., LaMoreaux, Werth, & Poole, 2001). However, the pain NRS evaluates only one dimension of the pain experienced (Hawker et al., 2011). Hence, it does not capture the complexity of the pain experienced or improvements due to symptom fluctuations.

Participants were asked three questions on the NRS. On a scale from 0 to 10 where 0 represents "no pain" and 10 represents "worst pain imaginable":

1. During the last 24 hours/week, how would you rate your knee pain at the highest?
2. During the last 24 hours/week, how would you rate your knee pain at the lowest?
3. During the last 24 hours/week, how would you rate your knee pain at average?

When patients were assessed daily they were asked about pain "during the last 24 hours", while when they were assessed weekly they were asked about pain "during the last week". See appendix 1 for the Norwegian translation.

4.5 Intervention

As mentioned, subjects in this study were already included in an ongoing randomized controlled trial (Oiestad et al., 2013) and therefore followed intervention as prescribed by that study. The intervention programs were either strength exercise or aerobic exercise and were guided by physiotherapists at selected physical therapy institutes in the Oslo and Akershus area. The programs lasted for 12 weeks with 2-3 training sessions per week. In addition, patients went through a pre-phase of 2 weeks to prepare for the intervention programs.

The strength exercise program contained exercises for quadriceps, hamstrings, hip abductors, hip extensors, and calf muscles. 8-10 repetitions maximum in 3 series with approximately 30 seconds to 1 minute pause between the series were performed. The aerobic program contained of 45 minutes ergometer cycling. Included in these 45 minutes were 10 minutes warm up, 30 minutes on moderate loading (75% of max heart

rate), and 5 minutes cool down. To ensure compliance, patients were asked to complete diaries which were controlled weekly by physiotherapists.

4.6 Statistical methods

Microsoft Excel was used for statistical analyses and for graphical presentation of the data. Data from the KOOS pain and the NRS for pain were presented graphically as time series for each subject. Data were described both individually and as a group. Describing data individually made it possible to evaluate each participants pain fluctuation through the baseline phase, intervention phase, and post intervention phase. Describing data as a group made it easier to compare to other studies, hence mean, minimum, and maximum values were described.

We chose to present the results from the KOOS pain and the NRS for pain by points. Since the KOOS is a 100 points scale and the NRS a 10 points scale, the results could easily be converted to percent. For example a 10 points change for the KOOS is also a 10 percent change for the KOOS. A 2 points change for the NRS for pain is a 20 percent change.

4.7 Ethical perspectives

The ongoing study (Oiestad et al., 2013) that this study was a part of was already approved by the Regional Ethical Committee and the Data Inspectorate in Norway (Ref. 2012/334). A notification for change was sent to the Regional Ethical Committee applying for the additional data collected in this study. This application was approved on July 2014 (Appendix 2).

Participation in the study was voluntary, and all subjects gave their approval of participation before inclusion (Appendix 3). The subjects were informed about the aims of the study, what participation implied, the right to withdrawal, potential benefit, potential inconvenience, and the rules for confidentiality.

5. Results

5.1 Subject characteristics at baseline

There were a total of eleven subjects that completed this study, eight males and three females. Subject 6 and 12 withdrew from the study and are not described in the results chapter. The average age among the subjects was 58 (from 45 to 67 years) and the average body mass index (BMI) was 28 (from 20 to 37). All subjects had Kellgren and Lawrence grade two or three.

***Table 4*:** Subject characteristics at baseline for each individual, mean, minimum, and maximum values.

Subject	1	2	3	4	5	7	8	9	10	11	13	μ	Min	Max
Age	62	56	54	55	60	66	57	45	65	67	51	58	45	67
Gender	M	M	M	M	M	M	F	F	M	M	F			
BMI	25	31	30	29	26	28	24	37	28	29	20	28	20	37
Years with symptoms	24	12	30	18	*	4	7	14	*	>30	6			

Subject 6 and 12 withdrew from the study.
** Subject 5 and 10 answered "many years" when asked about years with symptoms.*
Mean (μ), maximum (max) and minimum (min) scores are summarized on the right- hand side of the table.
BMI = Body mass index

At baseline, the mean KOOS scores were 58 (from 32 to 79) for the symptoms subscale, 63 (from 25 to 74) for the function in daily living subscale, 20 (from 0 to 40) for the function in sports and recreational activities subscale, and 32 (from 6 to 44) for the quality of life subscale.

***Tabel 5:** KOOS scores at baseline for each individual, mean, minimum, and maximum values.*

Subject	1	2	3	4	5	7	8	9	10	11	13	μ	Min	Max
KOOS symptom	79	46	75	75	61	79	32	32	68	50	39	58	32	79
KOOS ADL	74	25	72	69	84	68	35	72	66	34	91	63	25	74
KOOS Sport/rec	40	15	15	15	35	30	0	10	15	10	35	20	0	40
KOOS QOL	44	6	31	13	38	44	31	44	31	25	44	32	6	44

Subject 6 and 12 withdrew from the study.
KOOS = Knee injury and Osteoarthritis Outcome Score
ADL = Activities of daily living
Sport/rec = Sports and recreational activities
QOL = Quality of life

5.2 Assessments

The subjects completed on average 25 of the 28 assessments, which resulted in an average compliance of 89 percent. The subjects (subjects 1, 3, and 7) with the highest compliance completed 100 percent of the assessments while the subject (subject 13) with the lowest completed 71 percent of the assessments.

Table 6: *Subject compliance for each individual, mean, minimum, and maximum values.*

Subject	1	2	3	4	5	7	8	9	10	11	13	μ	Min	Max
Number of assessments completed	28	26	28	25	27	28	27	23	24	21	20	25	20	28
Compliance (%)	100	93	100	89	96	100	96	82	86	75	71	89	71	100

The table shows the number of assessments completed for each subject. The maximum number of possible assessments was 28 (7 at the baseline phase, 14 during the intervention phase, and 7 at the post intervention phase).
Subject 6 and 12 withdrew from the study.

5.3 Summary of results

The figure at the next page (figure 7) illustrates the KOOS pain scores for the eleven subjects during the baseline phase, the intervention phase and the post intervention phase. Pain fluctuated differently among the subjects. During the baseline phase, the mean fluctuation (difference between the lowest and highest score) in the KOOS pain scores was 20 points. During the intervention phase, the mean fluctuation was 28 points. During the post intervention phase, the mean fluctuation was 11 points. The subject with the highest fluctuation in score during the intervention phase was subject 4 who had 72 points fluctuation. The subjects with the lowest fluctuation were subject 9, 10, and 13 who had 11 points difference from the lowest to the highest score during the intervention phase.

The results showed that there was in general less pain fluctuations at the post intervention phase compared to the intervention phase and the baseline phase. All but one subject (subject 8) had higher fluctuations in the KOOS pain scores during the intervention phase compared to the post intervention phase. Comparing the post intervention phase with the baseline phase, all but two subjects (subject 8 and 11) had higher fluctuations in the KOOS pain scores at baseline phase compared to the post intervention phase. The trend lines showed that seven subjects had an increasing trend

from the baseline phase towards the post intervention phase. Four subjects had a decreasing trend.

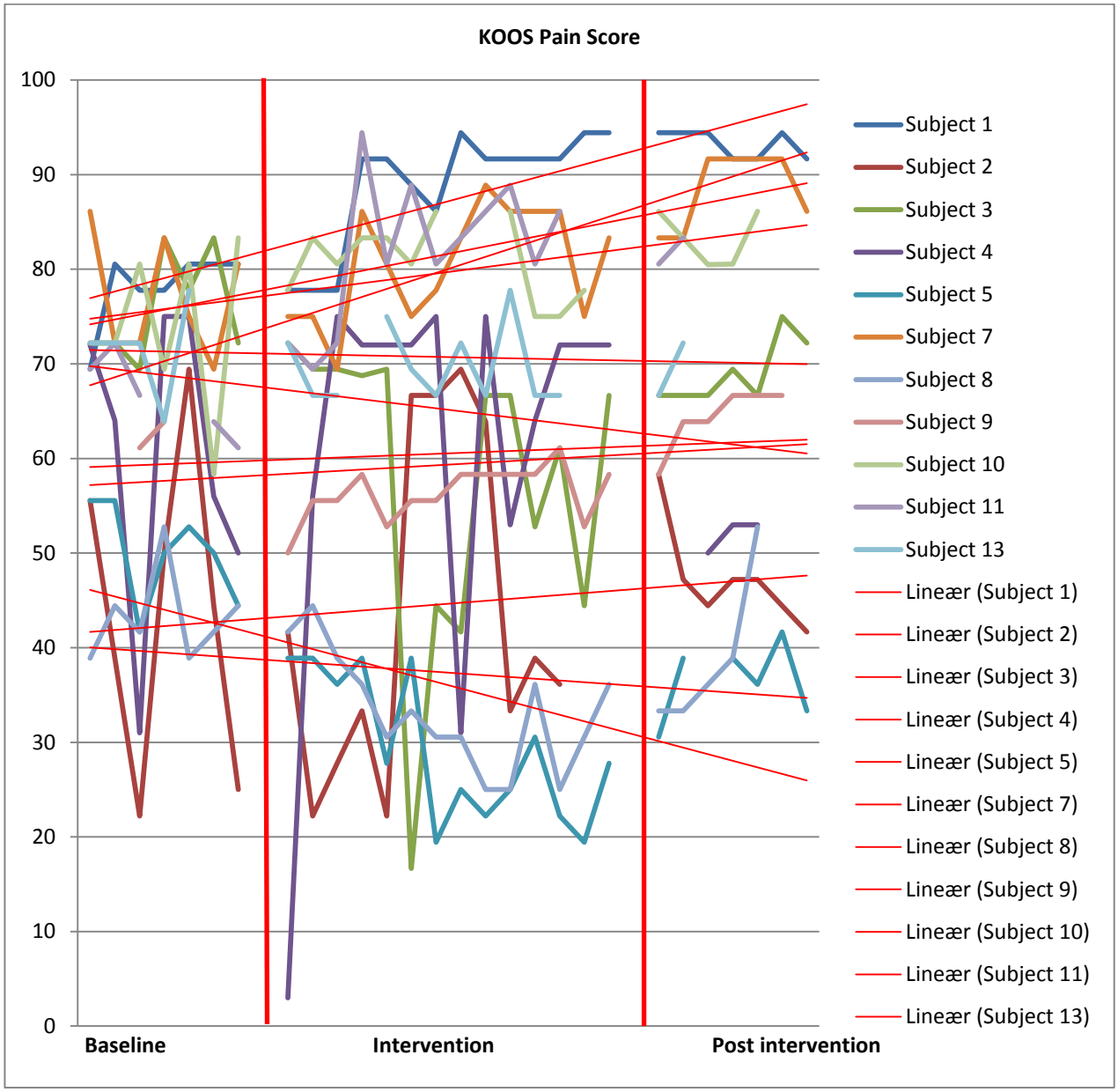


Figure 7: *KOOS Pain Score for each individual and trend lines during the baseline phase, the intervention phase, and the post intervention phase.*
The figure describes the KOOS pain scores for all the eleven subjects. For complete description of each subject individually see appendix 4.
KOOS = Knee injury and Osteoarthritis Outcome Score
Subject 6 and 12 withdrew from the study.

In this study, subjects were asked about their minimum, maximum and average pain the last 24hour/week at the NRS. The mean fluctuation (difference between the highest and lowest score) in the NRS for pain scores was 6 points during the baseline phase, 7 points during the intervention phase, and 3 points during the post intervention phase. The figure at the next page illustrates the scores from the question about pain in average during the last 24 hours/week at the NRS. For the minimum and maximum scores, see appendix 4. The scores from the question about average pain at NRS showed similarities with the KOOS pain scores. Pain fluctuated differently among the subjects and the pain fluctuations were less during the post intervention phase compared to the intervention phase and the baseline phase. The trend lines showed that eight subjects had an improvement in pain (decreasing trend) from the baseline phase towards the post intervention phase, while three subjects had a worsening (increasing trend) in pain.

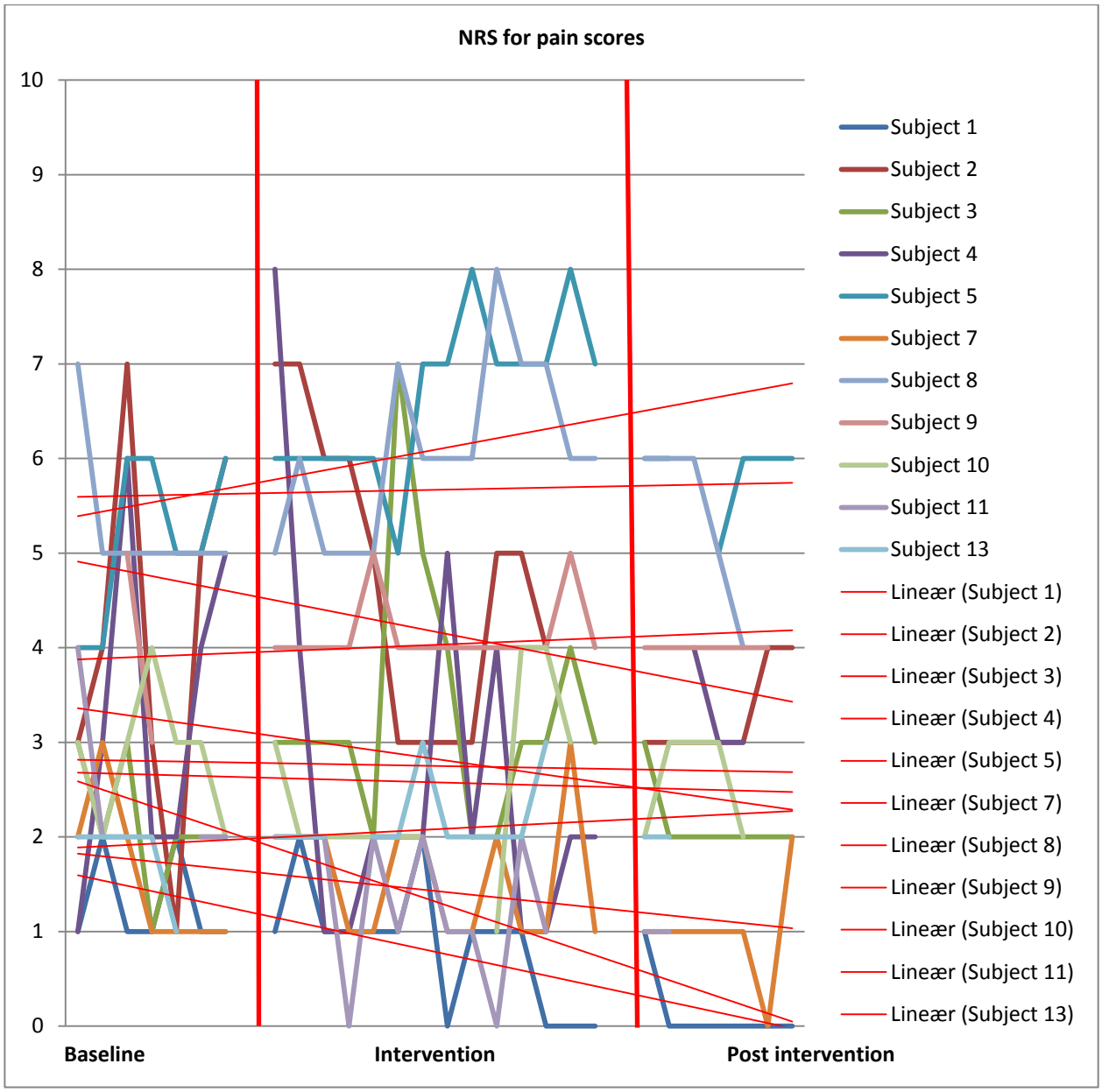


Figure 8: *NRS for pain scores for each individual and trend lines during the baseline phase, the intervention phase, and the post intervention phase..*
The figure describes scores from the question about pain in average during the last 24 hours/week at the NRS. It is important to notice that 0 represents "no pain" and 10 represents "worst pain imaginable". The scale is opposite of the KOOS scale. For complete description of each subject individually, see appendix 4.
NRS = Numeric Rating Scale
Subject 6 and 12 withdrew from the study.

5.4 Were baseline and post intervention KOOS pain scores in the ongoing randomized controlled trial (Oiestad et al., 2013) similar to KOOS pain scores in this study?

The figure below compares the baseline KOOS pain results from the randomized controlled trial (Oiestad et al., 2013) with the baseline KOOS pain results from this study. Five subjects (subject 4, 7, 8, 10, 13) had similar results, while six subjects (subject 1, 2, 3, 5, 9, 11) had results that differed ten points or more.

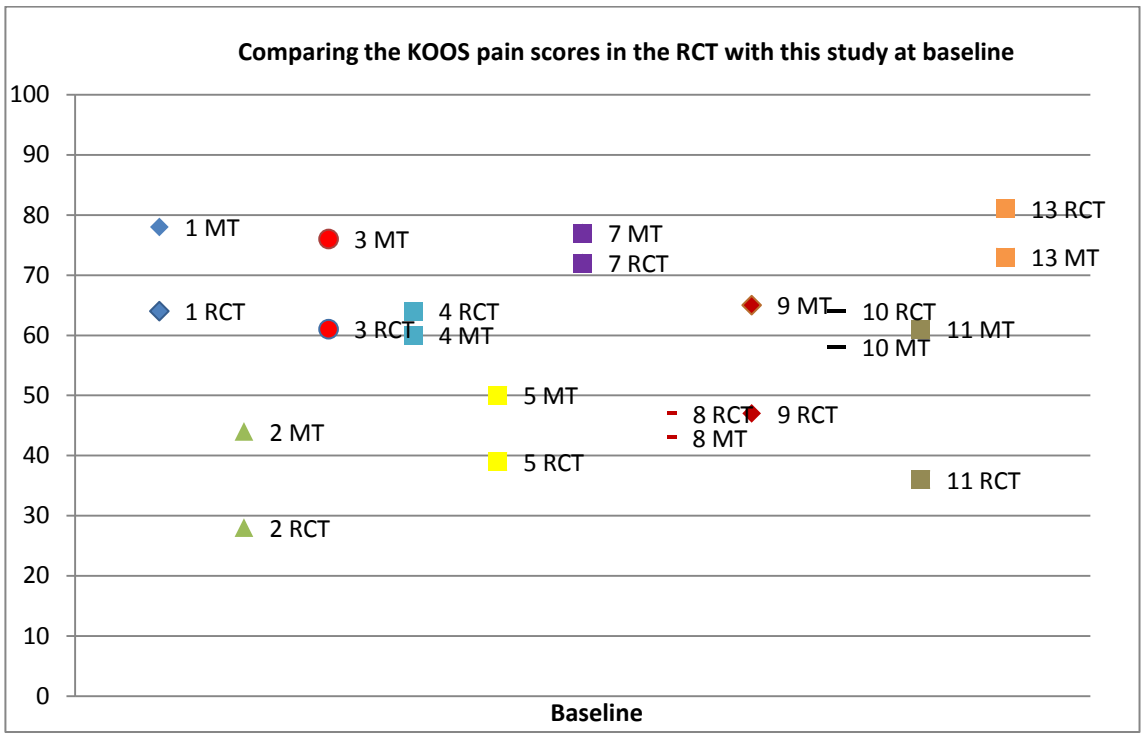


Figure 9: *Comparing baseline KOOS pain results from the randomized controlled trial (Oiestad et al., 2013) with this study.*
1,2,3 etc: Subject number 1, 2, 3 etc
RCT: Results from the randomized controlled trial at baseline (one assessment)
MT: Average scores at baseline (average of up to seven assessments) in this study
KOOS = Knee injury and Osteoarthritis Outcome Score

The figure below compares the post intervention KOOS pain results from the randomized controlled trial (Oiestad et al., 2013) with the post intervention KOOS pain results from this study. Seven subjects (subject 1, 2, 3, 5, 7, 9, 10) had similar results, while four subjects (subject 4, 8, 11, 13) had results that differed ten points or more.

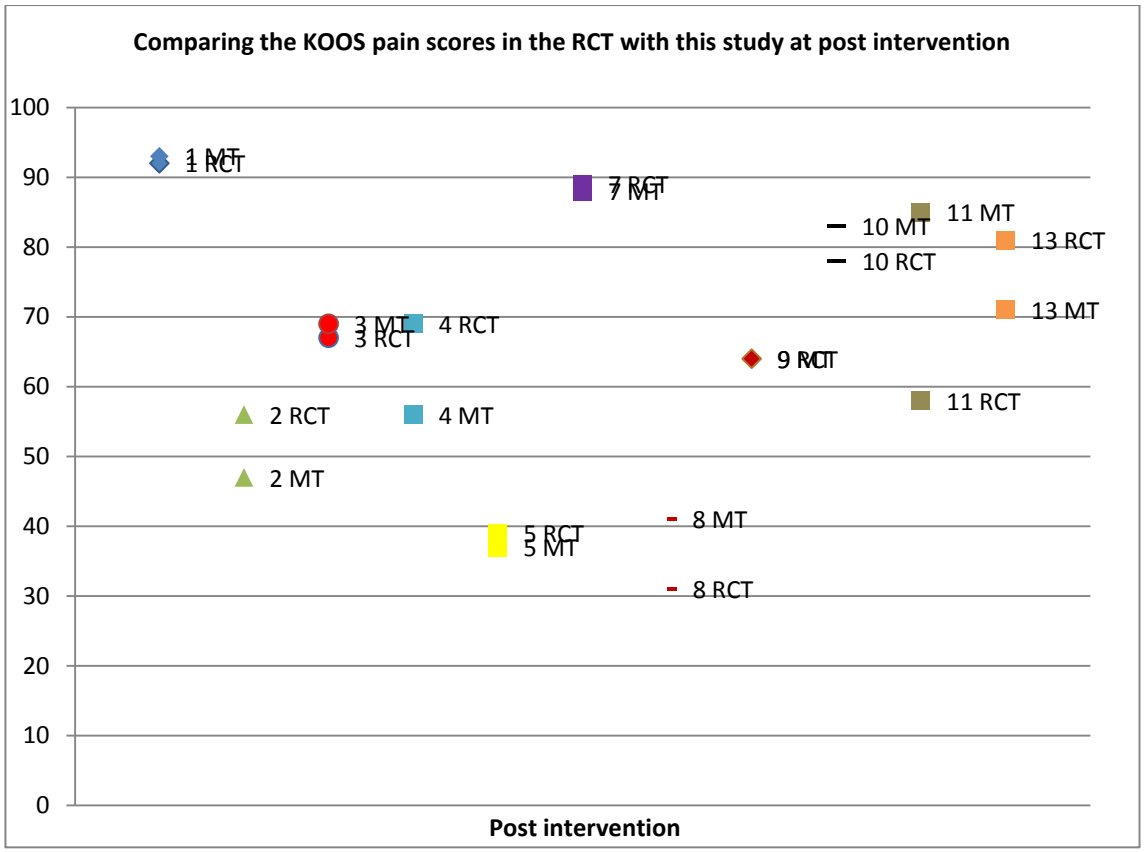


Figure 10: *Comparing the post intervention KOOS pain results from the randomized controlled trial (Oiestad et al., 2013) with this study.*

1,2,3 etc: *Subject number 1, 2, 3 etc*
RCT: *Results from the randomized controlled trial at post intervention (one assessment)*
MT: *Average scores at post intervention (average of up to seven assessments) in this study*
KOOS: *Knee injury and Osteoarthritis Outcome Score*

6. Discussion

The main purpose of this study was to evaluate how pain fluctuated over time among middle-aged patients with mild to moderate knee osteoarthritis undergoing a 14-week exercise intervention. The pain fluctuations (the difference between the highest and lowest score) varied substantially among the subjects during the intervention phase. The mean pain fluctuation during the intervention phase was 28 points measured with the KOOS pain and 7 points measured with the NRS for pain. Our hypothesis that pain fluctuations during the intervention phase would be 10 points or more for the KOOS pain and 2 points or more for the NRS for pain was confirmed for all subjects.

Our hypothesis that pain fluctuations would decrease at the post intervention phase compared to the baseline phase and the intervention phase was confirmed by the results from this study. Compared to the post intervention phase, pain fluctuation measured with the KOOS pain was higher during the intervention phase for all subjects, except one (subject 8). Measured with the NRS for pain, all subjects had higher pain fluctuation during the intervention phase compared to the post intervention phase. Comparing the post intervention phase with the baseline phase, all but two subjects (subject 8 and 11) had higher pain fluctuations at the baseline phase compared to the post intervention phase measured with the KOOS pain. Measured with the NRS for pain, all but one subject (subject 13) had higher pain fluctuations at the baseline phase compared to the post intervention phase. The trend lines for the KOOS pain showed that seven subjects had an increasing trend (pain improved) from baseline phase towards the post intervention phase, while four subjects had a decreasing trend (pain worsened). The trend lines for the average NRS for pain question showed that eight subjects had an improvement in pain (decreasing trend) from the baseline phase towards the post intervention phase, while three subjects had a worsening in pain (increasing trend).

In the last research question we compared the KOOS pain scores in the randomized controlled trial (Oiestad et al., 2013) with the KOOS pain scores in this study. At the baseline phase the KOOS pain scores were similar for five subjects (subject 4, 7, 8, 10, 13), while six subjects (subject 1, 2, 3, 5, 9, 11) had results that differed ten points or more. At the post intervention phase seven subjects (subject 1, 2, 3, 5, 7, 9, 10) had similar results, while four subjects (subject 4, 8, 11, 13) had results that differed ten

points or more. Our hypothesis that the results from our study would differ from the results in the randomized controlled trial, were not confirmed for all subjects.

In the following chapters the research questions and the methods will be discussed.

6.1 Discussion of results

6.1.1 How did pain fluctuate during the 14-weeks intervention?

The mean fluctuation at the KOOS pain during the 14-weeks intervention phase was 28 points. This is somewhat similar to within-day pain fluctuations found among patients with hand, hip, and knee osteoarthritis in a study by Allen et al. (2009). They found pain to fluctuate on average about 36 points on a scale from 0-100 tested on one weekday and one weekend day. The NRS for pain fluctuated more than the KOOS pain in this study. These differences between the NRS and the KOOS will be discussed in chapter 6.2.3 Outcome measures. On average, the NRS for pain fluctuated 7 points during the intervention phase, which is also considerably higher compared to a comparable study (Hutchings et al., 2007) where similar pain scales were included. Hutchings et al. (2007) found pain to fluctuate 4,3 points over a period of 12 weeks. However, the subjects in the study conducted by Hutchings et al. (2007) did not undergo an intervention which might explain some of the differences in the results from our study.

Pain fluctuation varied substantially among the eleven subjects. Three subjects in the upper end of the scale had pain fluctuations during the intervention phase of accordingly 72, 55, and 47 points for the KOOS pain. Their pain fluctuations for the NRS for pain were 10, 9 and 8. In the lower end of the scale three subjects had 11 points fluctuation for the KOOS pain during the intervention phase. For the NRS for pain the scores were 6, 4, and 4.

Based on the literature (Roos & Lohmander, 2003) that ten points change is a clinically relevant change (MCID) for the KOOS pain, we hypothesized that the subjects in our study would achieve this during the intervention phase. This hypothesis was confirmed, and all subjects had a clinical relevant change (MCID) according to this literature. However, according to another study (Ornetti et al., 2008) minimal detectable change (MDC) was found to be 13,4 points for the KOOS pain subscale. According to this cutoff, the results from the three subjects with the lowest pain fluctuations during the

intervention cannot be reliably distinguished from random error in the measurement (Lassere, van der Heijde, Johnson, Boers, & Edmonds, 2001). If we had used the cutoff of 13,4 points, the hypothesis would not have been confirmed for these three subjects.

As mentioned Farrar et al. (2001) found a reduction of approximately two points on the NRS to be clinically relevant (MCID) when assessing chronic pain intensity. According to this literature all our subjects had clinically meaningful changes on the NRS for pain during the intervention phase.

Why do pain fluctuations occur?

The literature describes pain fluctuations in patients with osteoarthritis, however why these pain fluctuations occur lack knowledge (Allen et al., 2009). In a study conducted by Focht et al. (2002), pain fluctuations were found to gradually increase throughout the day and reach their peak between 3 and 4 pm among older overweight or obese adults with knee osteoarthritis. This happened on a day with no exercise. These results suggest that osteoarthritis pain follow a natural or biological rhythm with peak pain fluctuations in the second half of the day. Bellamy et al. (2002) found similar results in their study investigating patients with hand osteoarthritis. They found pain fluctuations to change systematically throughout the day, suggesting that pain fluctuations were predictable. These subjects did not exercise either. However, this does not explain the big variations in pain fluctuations among the subjects found in this study.

Collins et al. (2014) also found pain to fluctuate over time in patients with knee osteoarthritis. However, the authors found pain to be relatively stable over the course of the six years follow up time. Their study found pain fluctuations to be relatively stable across the group of osteoarthritis patients, which is somewhat contrary to the results from this study. More in accordance with our results are the results from the study conducted by Leffrondre et al. (2004). They identified four pain fluctuation patterns among 835 subjects with osteoarthritis in the hip or the knee: (1) regularly increasing, (2) regularly decreasing, (3) stable, and (4) unstable with fluctuations. Similarly to our results, they found some patients to have high pain fluctuations while others had low. WOMAC was utilized as the measurement method in both studies (Collins, Katz, Dervan, & Losina, 2014; Leffondre et al., 2004), but the patients in the study conducted by Leffrondre et al. (2004) had more severe baseline symptoms compared to the patients

in the study conducted by Collins et al. (2014). Hence, comparing the results between these two studies must be done with caution.

The osteoarthritis population is heterogeneous, characterized by variable clinical features, biochemical and genetic characteristics, and responses to treatment (Driban, Sitler, Barbe, & Balasubramanian, 2010). It has been proposed that the heterogeneous osteoarthritis population could be divided into different subgroups or phenotypes (Felson, 2010). Hence, identifying different phenotypes in osteoarthritis patients may be of high importance to treatment and preventing development of the disease. Knoop et al. (2011) used clinically patient characteristics to identify phenotypes of knee osteoarthritis. The characteristics included radiographic osteoarthritis, muscle strength, body mass index and depression. On the basis of these characterizations Knoop et al. (2011) identified five phenotypes of knee osteoarthritis patients: " minimal joint disease phenotype", "strong muscle phenotype", "nonobese and weak muscle phenotype", "obese and weak muscle phenotype", and "depressive phenotype". They found the phenotypes "depressive phenotype" and "obese and weak muscle phenotype" to have higher pain levels and more severe activity limitations compared to the other three phenotypes. Unfortunately, we did not have enough data to determine which phenotype each subject belonged to. The phenotype could potentially have explained some of the variations in pain fluctuation among the subjects. Subject 9 could potentially have belonged to the phenotype "obese and weak muscle phenotype" since she had a BMI of 37. However, without data about her strength this must be considered with caution. Her pain fluctuation was among the lowest though, with 11 points fluctuation in the KOOS pain during the intervention period.

The etiology of pain fluctuations is not well understood (Zhang et al., 2011). Foss et al. (2006) suggested that pain fluctuations reflect the interaction between peripheral and central processes and the coping mechanisms that patients develop to deal best with the condition. Another feature associated to the pain fluctuations experienced in osteoarthritis are inflammation (Bonnet & Walsh, 2005). Both acute inflammation and chronic inflammation could contribute, and the symptoms differ between these two. Acute inflammation usually has a sudden onset, becoming apparent over minutes or hours, while chronic inflammation develops over a longer period of time and may persist for days, weeks, or even months. Zhang et al. (2011) examined the relationship

of changes in bone marrow lesions, effusion, and synovitis to fluctuation of knee pain among patients in the Multicenter Osteoarthritis study. They found changes in bone marrow lesions and synovitis to be associated with fluctuations in knee pain among the patients. Bone marrow lesions had the best predictive ability. These results might explain some of the acute pain incidents experienced by osteoarthritis patients.

Pain fluctuations has also been linked to fluctuation in psychological factors, however whether the pain influences the mood or vice versa is difficult to distinguish (Wise et al., 2010). Even though psychological factors can certainly contribute to a heightened pain experience, it is also a possibility that pain itself can contribute to poor mood (Neogi, 2013). A study conducted by Evers et al. (2014) found worrying and stress vulnerability to be linked to increased disease activity and symptoms in rheumatoid arthritis patients. Even though rheumatoid arthritis patients are different from osteoarthritis patients, some of the same mechanisms might be present in osteoarthritis patients.

6.1.2 Were pain fluctuations at baseline, during the 14-week intervention and at post intervention different from each other?

Starting with a new exercise program could potentially influence pain fluctuations in osteoarthritis patients. Osteoarthritis pain is typically exacerbated by activity and relieved by rest (Hunter et al., 2009), hence more fluctuations during the intervention phase was expected. This was expected especially in the beginning of the intervention phase when the intervention was introduced. Exercise may for some people lead to an increase in pain afterwards but the increase in pain are usually gone the day after exercise (Focht, Ewing, Gauvin, & Rejeski, 2002). A study of land-based exercise for patients with knee osteoarthritis indicated an increase in knee oedema following exercise (Rogind et al., 1998). The literature are clear regarding the positive effects of exercise for osteoarthritis of the knee though, (Fransen et al., 2015), therefore we expected pain fluctuations to decrease over time which it did. Pain fluctuations were lower at the post intervention phase compared to the baseline phase and the intervention phase.

Pain intensity

Interestingly, pain intensity measured with the KOOS pain was not clearly improving post intervention compared to baseline. Six subjects (subject 3 (76 vs 69), 4 (60 vs 56), 5 (50 vs 37), 8 (43 vs 41), 9 (65 vs 64), and 13(73 vs 71)) had better average KOOS pain scores at the baseline phase compared to the post intervention phase (see appendix 5). Thus, only five subjects had better KOOS pain scores at post intervention phase than at the baseline phase. If we look at the trend lines (see figure 7 and appendix 4) though, the trend is increasing for seven subjects while decreasing for four subjects. Meaning that according to the trend lines pain was improving for seven subjects and worsening for four subjects. The results were different if we look at the average NRS for pain scores, with three subjects (subject 5, 9, 13) having worse post intervention scores compared to baseline scores, while eight had better. The trend lines gave the same results with eight subjects improving in pain from the baseline phase towards the post intervention phase (decreasing trend), while three subjects were worsening in pain (increasing trend) (see figure 8).

The KOOS pain scores are different from what we could expect based on the literature documenting the positive effects of exercise for osteoarthritis of the knee (Fransen et al., 2015). Even though six subjects had worse average KOOS pain scores at post intervention compared to baseline, five of these subjects had differences of less than eight points. These small variations could be due to measurement errors and not necessarily due to clinical relevant changes. Nevertheless, one would expect the KOOS pain post intervention scores to be better considering the literature documenting the positive effects of exercise. The results from NRS for pain are in better accordance with the literature with most subjects having better post intervention scores compared to baseline scores. The numbers of patients are too low to draw any statistical conclusions. Therefore, these considerations must be interpreted with caution.

6.1.3 Were baseline and post intervention KOOS pain scores different from the KOOS pain scores these same individuals reported in the randomized controlled trial (Oiestad et al., 2013)?

Due to the growing literature documenting pain fluctuations in patients with osteoarthritis (Allen et al., 2009; Hutchings et al., 2007; Bellamy et al., 2002) we expected dissimilarity in the results between the randomized controlled trial (Oiestad et

al., 2013) and this study. When only having one assessment at baseline and one post intervention, the results might be different compared to one assessment daily for one week during the baseline phase and the post intervention phase. However, the results did not confirm our hypothesis for all the subjects. The results between the two studies were more similar than we expected.

At baseline and post intervention, subjects in the randomized controlled trial (Oiestad et al., 2013) were asked about the amount of pain during the last week while subjects in this study were asked about the amount of pain the last 24 hours. We expected to see more fluctuations in pain in this study since we asked about pain in a shorter timeframe. However, the results were similar (less than ten points difference for the KOOS pain) for five subjects at the baseline phase and seven subjects at the intervention phase.

Figure 9 and 10 describes average results at the baseline phase and the post intervention phase in this study compared to the one assessment at the baseline and the one assessment the post intervention in the randomized controlled trial. Allen et al. (2009) suggests that due to pain fluctuations, the day of the week which pain is assessed may affect the results. For example, assessing pain on the weekday when pain intensity is high may not be representative for the patients pain. Hence, which day you choose to assess pain may affect the results. Somewhat contrary, the results from this study might indicate that asking about the amount of pain the last week might give a relatively representative view of the patients pain intensity even though pain is fluctuating during that week.

6.2 Discussion of methods

6.2.1 Subjects

In this study, the mean BMI and age among osteoarthritis patients were similar to the data from international studies (Knoop et al., 2011). However, two subjects (9 and 13) were different with a BMI of respectively 37 and 20. This study included more than twice as many males than females. Considering osteoarthritis is more common among females than among males (Chaganti & Lane, 2011), the gender distribution was different than what was expected. The included subjects in this study had similar KOOS (all five subscales) scores at baseline compared to a newly published study of knee osteoarthritis patients (Henriksen et al., 2015). Compared to the subjects in another

study of knee osteoarthritis patients (Lund et al., 2008), our subjects had better scores for the KOOS subscales pain, symptom and activities of daily living. However, the subjects in our study had worse scores for sports and recreational activities and quality of life. This might indicate that the subjects in our study had higher expectations to what functional level they considered as good.

Years with symptoms varied considerably among the subjects; between four years (subject7) and more than 30 years (subject 11). In a study conducted by Hawker et al. (2008), patients described their pain as worsening over time, and being more related to activity in the early phase while being more constant in later phases of osteoarthritis. Based on this literature, pain fluctuation should be different between these two subjects in our study. However, this was not the case. The results were similar for subject 7 and 11 in which subject 7 fluctuated 20 points for the KOOS pain during the intervention phase while subject 11 fluctuated 25 points.

In summary, subjects in this study were representative for the osteoarthritis population according to age and BMI. The duration of symptoms varied between the subjects, from four years to more than 30 years. The gender distribution was not representative for the osteoarthritis population, with more than twice as many males than females. All subjects had Kellgren and Lawrence grade two or three.

6.2.2 Study design

Since the overall purpose of this study was to evaluate pain fluctuations among patients with knee osteoarthritis undergoing an exercise intervention, a single subject design was found appropriate with repeated measurements. To be able to evaluate patients pain fluctuations we needed to collect information about each individual patient while they underwent the exercise intervention. The single subject design permit collection of data during an intervention period while the treatment is being delivered (Ottenbacher & York, 1984). Moreover, we needed repeated measurements at the baseline phase, the intervention phase, and the post intervention phase to be able to evaluate the fluctuating nature of the patients pain. Typically group designs only measures participants a few times within the study, making the researcher unable to determine the typical pattern of fluctuation (Carter et al., 2011). Group designs often measure patients only one time at baseline and one time post intervention. The results then may be due to a natural

fluctuation and not necessarily a real change. Single subject designs are characterized by extended periods of measurements making it possible to determine the pattern of fluctuation. The lack of a control group was a threat to the internal validity, but the repeated measurements at baseline allowed us to discount most of the threats to the internal validity (Engel & Schutt, 2005).

AB design is the most basic and has been described as the foundation of single subject designs, where A is representing baseline and B intervention (Backman et al., 1997). Different variations of the AB design exist. An extension of the AB design is the ABA design where the intervention is withdrawn in the third phase (Ottenbacher & York, 1984). This design is also referred to as withdrawal designs (Engel & Schutt, 2005). In our study a post intervention period was added in the end, which made this an ABA design. The withdrawal of the intervention provides greater confidence in determining the effect of the intervention (Ottenbacher & York, 1984). However, we did not control if patients stopped doing exercise after the intervention which means they might have continued exercising.

The limited time for this study made it impossible to include a large number of participants. Group designs require usually larger sample sizes to detect differences between the groups. Single-subject designs may be used when the number of subjects are low (Carter et al., 2011). The participants had big variations in pain fluctuations which made it interesting to follow them individually instead as a group. Group designs are not designed to follow participants individually. A limitation with single subject deigns however, are the generalizability of results which may be low (Carter et al., 2011). Engel & Schutt (2005) asks: "How is evidence about that single individual relevant to other clients?" To counter this limitation, single subject designs should be replicated across multiple subjects in different clinical settings according to Backman et al. (1997). Our results are first and foremost descriptive for the eleven subjects included in this study. To be able to say something about osteoarthritis patients in general, more and larger studies are needed.

The aim was to give a descriptive view of pain fluctuations, hence patients were followed over a period of time. To be able to give a representative picture of patients daily pain fluctuations, at least four days of pain recordings should be obtained

according to Jensen & McFarland (1993). In this study we included seven days of pain recordings at both baseline and post intervention. It is in accordance with earlier studies describing daily pain fluctuations in patients with osteoarthritis, which included respectively two days (Allen et al., 2009) and ten days (Bellamy et al., 2002) of pain assessments. However, this study included only one pain assessment per day while earlier studies included seven (Allen et al., 2009) and six (Bellamy et al., 2002) respectively pain assessments per day. According to Engel & Schutt (2005) a general rule is that more data points will increase your certainty about the pattern. Hence, the results of this study might have been more accurate for patients pain fluctuations with more assessments per day. Due to the amount of resources needed and the scope of this study, it was decided to only make one pain assessment daily.

It was attempted to do the daily pain assessments at the same time of the day for the individual patient. However, this was found difficult. Patients did not always answer the phone immediately, making it difficult to keep a structured timetable. The result was different time intervals between the daily pain assessments, which possibly influenced the results since current pain levels may affect pain recall (Jensen, Mardekian, Lakshminarayanan, & Boye, 2008). This could have been arranged before the telephone interview started by creating a schedule for when the patients could be contacted.

During the intervention period in the randomized controlled trial (Oiestad et al., 2013) we assessed pain fluctuation once a week. The Longitudinal Examination of Arthritis Pain Study (Hutchings et al., 2007) has earlier described weekly pain fluctuations among hip or knee osteoarthritis patients by assessing pain levels once a week. According to the Longitudinal Examination of Arthritis Pain Study (Hutchings et al., 2007) they were the first study to describe longitudinal relationships between weekly changes in pain levels and other health outcomes in adults with osteoarthritis.

Patients could choose to answer questionnaires either by telephone or by email. Only one patient chose to reply by email. Patients who chose to answer by telephone did not have a copy of the questionnaires in front of them. Hence, they could not forward fill their answers. However, it is possible they remembered their last answer due to the short timeframe between the assessments. The subject who replied by email received a

new questionnaire for every new assessment. The questionnaire was dated to ensure that a copy of the last questionnaire was not forwarded.

6.2.3 Outcome measures

Knee Injury and Osteoarthritis Outcome Score

The KOOS has undergone a substantial amount of psychometric testing, and has been established as a reliable and valid measure for patients with knee osteoarthritis (Collins, Misra, Felson, Crossley, & Roos, 2011). The use of individual scores for each subscale, rather than an aggregate score, makes it easy to get an overview on different dimensions which are important since osteoarthritis patients are a heterogenic population. However, it has not been validated for use during telephone interviews (Collins et al., 2011). Therefore, caution is needed when interpreting results from this study.

Another limitation by using the KOOS is that patients are reporting answers by memory, which creates a risk for recall bias. When people are recalling from memory, it creates a risk for systematic errors (Laake, Olsen, & Benestad, 2008). The short time that patients had to recall (one week or 24 hour) makes the risk of recall bias less.

Numeric Rating Scale for Pain

The NRS for pain has been observed as a reliable and valid tool for detecting changes in pain intensity in rheumatic disease and chronic pain conditions (Hawker et al., 2011). This also includes when the NRS for pain is utilized during telephone interviews. Like all self reported answers by memory, the risk of recall bias is also present for the NRS for pain.

Comparing KOOS and NRS

As mentioned, the results for the KOOS pain and the NRS for pain demonstrated some differences. One basic difference between these two assessments tools is the way the questions are asked. The KOOS pain is focusing on pain related to an activity, while the NRS for pain in this study was focusing on pain in general. Asking a person how much pain they experienced related to an activity is different from asking a person about how much pain they experienced in general. Hence, the results from these two measurements might be different.

Another difference between the KOOS pain and the NRS for pain in our study was the timeframe of the questions. When utilizing the KOOS pain, subjects were asked about the amount of pain either the last week or the last 24 hours. This could be interpreted as the amount of pain on average during the last week or the last 24 hours. When utilizing the NRS for pain, subjects were asked three questions. They were asked about the minimum, maximum and average pain during the last week or 24 hours. Asking about maximum and minimum pain could potentially give more fluctuations in answers compared to asking about the amount of pain. Therefore, the question about average pain for NRS might be more similar to the KOOS pain questions. Hence, this might be the reason why the results from the average NRS for pain (when not including maximum and minimum NRS) were more similar to the results from the KOOS pain.

The way these to measurements are scored are also different. At the KOOS a higher score indicate lower pain intensity, while at the NRS for pain a higher score indicate higher pain intensity. This is important to remember when interpreting the graphs (figure 7, 8, and appendix 4) with the results from the KOOS pain and the NRS for pain.

6.2.4 How the data was presented

Visual analysis of data is the traditional method used in single subject design research (Wolery & Harris, 1982). Since single-subject designs emphasize the examination of a subjects individual fluctuations of performance, and because of the rules for using statistical analyses of subject data, visual analysis is the favored method of evaluating results in single subject designs (Carter et al., 2011). Hence, the results from our study were also presented in a visual manner. By creating time series for each subject, trends, levels, and variability for each subject's results were visualized. Level is the difference between two assessments. Trend is the direction of change of the results, and could be increasing, decreasing, or cyclical. Variability means how different or divergent the scores are within a baseline or intervention phase (Engel & Schutt, 2005). By visually analyzing the lines going through the data points you could interpret the direction of the trend. A trend line was added to the graphs making it easier to visualize the trends of the results (see figure 7, 8, and appendix 4).

There is a possibility that results presented visually may be interpreted by the reader inconsistently (Ottenbacher & York, 1984). To meet this problem results should be

analyzed both statistically and visually according to Ottenbacher & York (1984). Therefore, results from this study were also presented by numbers in addition to visual presentations (see appendix 5 and 6).

6.3 Clinical implications

This single subject design study has shown that there are large variations in pain fluctuations among patients with knee osteoarthritis. Even though patients may be similar in BMI, age, and Kellgren and Lawrence grade of osteoarthritis, their pain fluctuations might be very diverse. Some patients had high pain fluctuations, while other patients had more stable pain fluctuations. It is important to remember that fluctuations in pain are normal when treating and evaluating osteoarthritis patients, both in the clinic and in research. It is also important to inform the patients about the fluctuating nature of osteoarthritis pain. Assessing individuals patterns of pain fluctuations can help with recommendations for timing of treatment (Allen et al., 2009).

6.4 Future research

If we could predict which patients who would have high pain fluctuations we could easier adjust treatment to the individual needs. Studies looking at what characterizes the patients with high pain fluctuations could potentially answer this question. For example a certain phenotype of osteoarthritis patients may have high pain fluctuations.

7. Conclusion

This study showed that overall, according to a cutoff of ten points for the KOOS pain and two points for the NRS for pain patients with knee osteoarthritis reported clinically meaningful (CMID) pain fluctuations during a 14-week intervention period. Pain fluctuations varied substantially among the eleven subjects. Some patients had high pain fluctuations while others had more stable pain fluctuations. In general, pain fluctuated less at the post intervention compared to the baseline and during the intervention. The results from this study add to the literature documenting pain fluctuations in patients with knee osteoarthritis.

Reference List

Allen, K. D., Coffman, C. J., Golightly, Y. M., Stechuchak, K. M., & Keefe, F. J. (2009). Daily pain variations among patients with hand, hip, and knee osteoarthritis. *Osteoarthritis.Cartilage., 17,* 1275-1282.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K. et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and Rheumatism, 29,* 1039-1049.

Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. *Progress in Neurobiology, 87,* 81-97.

Ashraf, S., Wibberley, H., Mapp, P. I., Hill, R., Wilson, D., & Walsh, D. A. (2011). Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. *Annals of the Rheumatic Diseases, 70,* 523-529.

Backman, C. L., Harris, S. R., Chisholm, J. A., & Monette, A. D. (1997). Single-subject research in rehabilitation: a review of studies using AB, withdrawal, multiple baseline, and alternating treatments designs. *Archives of Physical Medicine and Rehabilitation, 78,* 1145-1153.

Bandura, A. (1986). *Social foundations of thought and action: a social cognitive theory*. Englewood Cliffs, N.J.: Prentice-Hall.

Bartels, E. M., Lund, H., Hagen, K. B., Dagfinrud, H., Christensen, R., & Danneskiold-Samsoe, B. (2007). Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane.Database.Syst.Rev.,* CD005523.

Beckwee, D., Vaes, P., Cnudde, M., Swinnen, E., & Bautmans, I. (2013). Osteoarthritis of the knee: why does exercise work? A qualitative study of the literature. *Ageing Res.Rev., 12,* 226-236.

Bedson, J. & Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC.Musculoskelet.Disord., 9,* 116.

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *Journal of Rheumatology, 15,* 1833-1840.

Bellamy, N., Sothern, R. B., Campbell, J., & Buchanan, W. W. (2002). Rhythmic variations in pain, stiffness, and manual dexterity in hand osteoarthritis. *Annals of the Rheumatic Diseases, 61,* 1075-1080.

Bennell, K. L., Wrigley, T. V., Hunt, M. A., Lim, B. W., & Hinman, R. S. (2013). Update on the role of muscle in the genesis and management of knee osteoarthritis. *Rheumatic Diseases Clinics of North America, 39,* 145-176.

Berenbaum, F. (2013). Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis.Cartilage., 21,* 16-21.

Bhattacharyya, T., Gale, D., Dewire, P., Totterman, S., Gale, M. E., McLaughlin, S. et al. (2003). The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. *Journal of Bone and Joint Surgery, 85-A,* 4-9.

Bijlsma, J. W., Berenbaum, F., & Lafeber, F. P. (2011). Osteoarthritis: an update with relevance for clinical practice. *Lancet, 377,* 2115-2126.

Bliddal, H., Leeds, A. R., & Christensen, R. (2014). Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. *Obes.Rev., 15,* 578-586.

Bonnet, C. S. & Walsh, D. A. (2005). Osteoarthritis, angiogenesis and inflammation. *Rheumatology.(Oxford), 44,* 7-16.

Brandt, K. D., Dieppe, P., & Radin, E. L. (2008). Etiopathogenesis of osteoarthritis. *Rheumatic Diseases Clinics of North America, 34,* 531-559.

Brekke, M., Hjortdahl, P., & Kvien, T. K. (2003). Changes in self-efficacy and health status over 5 years: a longitudinal observational study of 306 patients with rheumatoid arthritis. *Arthritis and Rheumatism, 49,* 342-348.

Buckwalter, J. A. & Martin, J. A. (2006). Osteoarthritis. *Adv.Drug Deliv.Rev., 58,* 150-167.

Carter, R. E., Lubinsky, J., & Domholdt, E. (2011). *Rehabilitation research: principles and applications*. (vols. 4th ed.) St. Louis, Miss.: Elsevier Saunders.

Chaganti, R. K. & Lane, N. E. (2011). Risk factors for incident osteoarthritis of the hip and knee. *Curr.Rev.Musculoskelet.Med., 4,* 99-104.

Cibere, J. (2006). Do we need radiographs to diagnose osteoarthritis? *Best.Pract.Res.Clin.Rheumatol., 20,* 27-38.

Cicuttini, F. M. & Wluka, A. E. (2014). Osteoarthritis: Is OA a mechanical or systemic disease? *Nat.Rev.Rheumatol., 10,* 515-516.

Collins, J. E., Katz, J. N., Dervan, E. E., & Losina, E. (2014). Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis.Cartilage., 22,* 622-630.

Collins, N. J., Misra, D., Felson, D. T., Crossley, K. M., & Roos, E. M. (2011). Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res.(Hoboken.), 63 Suppl 11,* S208-S228.

Dieppe, P. A. & Lohmander, L. S. (2005). Pathogenesis and management of pain in osteoarthritis. *Lancet, 365,* 965-973.

Dimitroulas, T., Duarte, R. V., Behura, A., Kitas, G. D., & Raphael, J. H. (2014). Neuropathic pain in osteoarthritis: A review of pathophysiological mechanisms and implications for treatment. *Seminars in Arthritis and Rheumatism*.

Driban, J. B., Sitler, M. R., Barbe, M. F., & Balasubramanian, E. (2010). Is osteoarthritis a heterogeneous disease that can be stratified into subsets? *Clinical Rheumatology, 29,* 123-131.

Ehrich, E. W., Davies, G. M., Watson, D. J., Bolognese, J. A., Seidenberg, B. C., & Bellamy, N. (2000). Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. *Journal of Rheumatology, 27,* 2635-2641.

Engel, R. J. & Schutt, R. K. (2005). *The practice of research in social work.* Thousand Oaks, Calif.: Sage.

Evers, A. W., Verhoeven, E. W., van, M. H., Sweep, F. C., Kraaimaat, F. W., Donders, A. R. et al. (2014). Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. *Annals of the Rheumatic Diseases, 73,* 1683-1688.

Farrar, J. T., Young, J. P., Jr., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain, 94,* 149-158.

Felson, D. T. (2005). The sources of pain in knee osteoarthritis. *Current Opinion in Rheumatology, 17,* 624-628.

Felson, D. T. (2010). Identifying different osteoarthritis phenotypes through epidemiology. *Osteoarthritis.Cartilage., 18,* 601-604.

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis.Cartilage., 21,* 10-15.

Felson, D. T., Lawrence, R. C., Hochberg, M. C., McAlindon, T., Dieppe, P. A., Minor, M. A. et al. (2000). Osteoarthritis: new insights. Part 2: treatment approaches. *Annals of Internal Medicine, 133,* 726-737.

Felson, D. T., Niu, J., Guermazi, A., Sack, B., & Aliabadi, P. (2011). Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. *Annals of the Rheumatic Diseases, 70,* 1884-1886.

Fernandes, L., Hagen, K. B., Bijlsma, J. W., Andreassen, O., Christensen, P., Conaghan, P. G. et al. (2013). EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Annals of the Rheumatic Diseases, 72,* 1125-1135.

Flugsrud, G. B., Nordsletten, L., Reinholt, F. P., Risberg, M. A., Rydevik, K., & Uhlig, T. (2010). [Osteoarthritis]. *Tidsskr.Nor Laegeforen., 130,* 2136-2140.

Focht, B. C., Ewing, V., Gauvin, L., & Rejeski, W. J. (2002). The unique and transient impact of acute exercise on pain perception in older, overweight, or obese adults with knee osteoarthritis. *Annals of Behavioral Medicine, 24,* 201-210.

Foss, J. M., Apkarian, A. V., & Chialvo, D. R. (2006). Dynamics of pain: fractal dimension of temporal variability of spontaneous pain differentiates between pain States. *Journal of Neurophysiology, 95,* 730-736.

Fransen, M. & McConnell, S. (2008). Exercise for osteoarthritis of the knee. *Cochrane.Database.Syst.Rev.,* CD004376.

Fransen, M., McConnell, S., Harmer, A. R., Van der Esch, M., Simic, M., & Bennell, K. L. (2015). Exercise for osteoarthritis of the knee. *Cochrane Database Syst.Rev., 1,* CD004376.

Gooberman-Hill, R., Woolhead, G., Mackichan, F., Ayis, S., Williams, S., & Dieppe, P. (2007). Assessing chronic joint pain: lessons from a focus group study. *Arthritis and Rheumatism, 57,* 666-671.

Grotle, M., Hagen, K. B., Natvig, B., Dahl, F. A., & Kvien, T. K. (2008). Prevalence and burden of osteoarthritis: results from a population survey in Norway. *Journal of Rheumatology, 35,* 677-684.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A. et al. (2005). Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. *Crit Pathw.Cardiol., 4,* 198-203.

Gupta, S., Hawker, G. A., Laporte, A., Croxford, R., & Coyte, P. C. (2005). The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology.(Oxford), 44,* 1531-1537.

Hagen, K. B., Dagfinrud, H., Moe, R. H., Osteras, N., Kjeken, I., Grotle, M. et al. (2012). Exercise therapy for bone and muscle health: an overview of systematic reviews. *BMC.Med., 10,* 167.

Han, C. D., Yang, I. H., Lee, W. S., Park, Y. J., & Park, K. K. (2013). Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). *BMC.Public Health, 13,* 603.

Hansson, P. (2014). Translational aspects of central sensitization induced by primary afferent activity: what it is and what it is not. *Pain, 155,* 1932-1934.

Haringman, J. J., Ludikhuize, J., & Tak, P. P. (2004). Chemokines in joint disease: the key to inflammation? *Annals of the Rheumatic Diseases, 63,* 1186-1194.

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res.(Hoboken.), 63 Suppl 11,* S240-S252.

Hawker, G. A., Stewart, L., French, M. R., Cibere, J., Jordan, J. M., March, L. et al. (2008). Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis.Cartilage., 16,* 415-422.

Henriksen, M., Christensen, R., Klokker, L., Bartholdy, C., Bandak, E., Ellegaard, K. et al. (2015). Evaluation of the Benefit of Corticosteroid Injection Before Exercise Therapy in Patients With Osteoarthritis of the Knee: A Randomized Clinical Trial. *JAMA Intern.Med.*.

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J. et al. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.(Hoboken.), 64,* 465-474.

Hunt, M. A., Birmingham, T. B., Skarakis-Doyle, E., & Vandervoort, A. A. (2008). Towards a biopsychosocial framework of osteoarthritis of the knee. *Disability and Rehabilitation, 30,* 54-61.

Hunter, D. J. (2011). Osteoarthritis. *Best.Pract.Res.Clin.Rheumatol., 25,* 801-814.

Hunter, D. J. & Eckstein, F. (2009). Exercise and osteoarthritis. *Journal of Anatomy, 214,* 197-207.

Hunter, D. J. & Felson, D. T. (2006). Osteoarthritis. *BMJ, 332,* 639-642.

Hunter, D. J., Guermazi, A., Roemer, F., Zhang, Y., & Neogi, T. (2013). Structural correlates of pain in joints with osteoarthritis. *Osteoarthritis.Cartilage., 21,* 1170-1178.

Hunter, D. J., McDougall, J. J., & Keefe, F. J. (2009). The symptoms of osteoarthritis and the genesis of pain. *Medical Clinics of North America, 93,* 83-100, xi.

Hutchings, A., Calloway, M., Choy, E., Hooper, M., Hunter, D. J., Jordan, J. M. et al. (2007). The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *Journal of Rheumatology, 34,* 2291-2300.

IASP (1986). Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain Suppl, 3,* S1-226.

Jamtvedt, G., Dahm, K. T., Christie, A., Moe, R. H., Haavardsholm, E., Holm, I. et al. (2008). Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Physical Therapy, 88,* 123-136.

Jensen, M. P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: a comparison of six methods. *Pain, 27,* 117-126.

Jensen, M. P., Mardekian, J., Lakshminarayanan, M., & Boye, M. E. (2008). Validity of 24-h recall ratings of pain severity: biasing effects of "Peak" and "End" pain. *Pain, 137,* 422-427.

Jensen, M. P. & McFarland, C. A. (1993). Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain, 55,* 195-203.

Johnson, V. L. & Hunter, D. J. (2014). The epidemiology of osteoarthritis. *Best.Pract.Res.Clin.Rheumatol., 28,* 5-15.

Juhl, C., Christensen, R., Roos, E. M., Zhang, W., & Lund, H. (2014). Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol., 66,* 622-636.

KELLGREN, J. H. & LAWRENCE, J. S. (1957). Radiological assessment of osteo-arthrosis. *Annals of the Rheumatic Diseases, 16,* 494-502.

Knoop, J., van der Leeden, M., Thorstensson, C. A., Roorda, L. D., Lems, W. F., Knol, D. L. et al. (2011). Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res.(Hoboken.), 63,* 1535-1542.

Konttinen, Y. T., Sillat, T., Barreto, G., Ainola, M., & Nordstrom, D. C. (2012). Osteoarthritis as an autoinflammatory disease caused by chondrocyte-mediated inflammatory responses. *Arthritis and Rheumatism, 64,* 613-616.

Kroon, F. P., van der Burg, L. R., Buchbinder, R., Osborne, R. H., Johnston, R. V., & Pitt, V. (2014). Self-management education programmes for osteoarthritis. *Cochrane.Database.Syst.Rev., 1,* CD008963.

Laake, P., Olsen, B. r. R., & Benestad, H. B. (2008). *Forskning i medisin og biofag*. (vols. 2. utg.) Oslo: Gyldendal akademisk.

Lassere, M. N., van der Heijde, D., Johnson, K. R., Boers, M., & Edmonds, J. (2001). Reliability of measures of disease activity and disease damage in rheumatoid arthritis: implications for smallest detectable difference, minimal clinically important difference, and analysis of treatment effects in randomized controlled trials. *Journal of Rheumatology, 28,* 892-903.

Latremoliere, A. & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J.Pain, 10,* 895-926.

Lawrence, R. C., Helmick, C. G., Arnett, F. C., Deyo, R. A., Felson, D. T., Giannini, E. H. et al. (1998). Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and Rheumatism, 41,* 778-799.

Leffondre, K., Abrahamowicz, M., Regeasse, A., Hawker, G. A., Badley, E. M., McCusker, J. et al. (2004). Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *Journal of Clinical Epidemiology, 57,* 1049-1062.

Lluch, G. E., Nijs, J., Torres-Cueco, R., & Lopez, C. C. (2013). Pain treatment for patients with osteoarthritis and central sensitization. *Physical Therapy, 93,* 842-851.

Lohmander, L. S. & Roos, E. M. (2007). Clinical update: treating osteoarthritis. *Lancet, 370,* 2082-2084.

Lorig, K., Chastain, R. L., Ung, E., Shoor, S., & Holman, H. R. (1989). Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis and Rheumatism, 32,* 37-44.

Losina, E., Weinstein, A. M., Reichmann, W. M., Burbine, S. A., Solomon, D. H., Daigle, M. E. et al. (2013). Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res.(Hoboken.), 65,* 703-711.

Lund, H., Weile, U., Christensen, R., Rostock, B., Downey, A., Bartels, E. M. et al. (2008). A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. *J.Rehabil.Med., 40,* 137-144.

Magliano, M. (2008). Obesity and arthritis. *Menopause.Int., 14,* 149-154.

Maly, M. R., Costigan, P. A., & Olney, S. J. (2008). Mechanical factors relate to pain in knee osteoarthritis. *Clin.Biomech.(Bristol., Avon.), 23,* 796-805.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M. et al. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis.Cartilage., 22,* 363-388.

Mease, P. J., Hanna, S., Frakes, E. P., & Altman, R. D. (2011). Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *Journal of Rheumatology, 38,* 1546-1551.

Merskey, H. & Bogduk, N. (1994). *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. (vols. 2nd ed.) Seattle: IASP Press.

Messier, S. P., Gutekunst, D. J., Davis, C., & DeVita, P. (2005). Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis and Rheumatism, 52,* 2026-2032.

Messier, S. P., Legault, C., Mihalko, S., Miller, G. D., Loeser, R. F., DeVita, P. et al. (2009). The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. *BMC.Musculoskelet.Disord., 10,* 93.

Messier, S. P., Loeser, R. F., Miller, G. D., Morgan, T. M., Rejeski, W. J., Sevick, M. A. et al. (2004). Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis and Rheumatism, 50,* 1501-1510.

Monira, H. S., Wang, Y., Cicuttini, F. M., Simpson, J. A., Giles, G. G., Graves, S. et al. (2014). Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. *Seminars in Arthritis and Rheumatism, 43,* 429-436.

Murphy, L., Schwartz, T. A., Helmick, C. G., Renner, J. B., Tudor, G., Koch, G. et al. (2008). Lifetime risk of symptomatic knee osteoarthritis. *Arthritis and Rheumatism, 59,* 1207-1213.

Murphy, S. L., Phillips, K., Williams, D. A., & Clauw, D. J. (2012). The role of the central nervous system in osteoarthritis pain and implications for rehabilitation. *Curr.Rheumatol.Rep., 14,* 576-582.

Nasjonalt kompetansesenter for leddproteser (2009). Rapport. *Nasjonalt register for leddproteser*.

Nasjonalt kompetansesenter for leddproteser (2014). Rapport. *Nasjonalt register for leddproteser*.

Nelson, A. E., Allen, K. D., Golightly, Y. M., Goode, A. P., & Jordan, J. M. (2013). A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. *Seminars in Arthritis and Rheumatism*.

Nelson, A. E., Allen, K. D., Golightly, Y. M., Goode, A. P., & Jordan, J. M. (2014). A systematic review of recommendations and guidelines for the management of osteoarthritis: The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. *Seminars in Arthritis and Rheumatism, 43,* 701-712.

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis.Cartilage., 21,* 1145-1153.

Nuki, G. (1999). Osteoarthritis: a problem of joint failure. *Zeitschrift fur Rheumatologie, 58,* 142-147.

O'Reilly, S. C., Muir, K. R., & Doherty, M. (1999). Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Annals of the Rheumatic Diseases, 58,* 15-19.

Oiestad, B. E., Osteras, N., Frobell, R., Grotle, M., Brogger, H., & Risberg, M. A. (2013). Efficacy of strength and aerobic exercise on patient-reported outcomes and

structural changes in patients with knee osteoarthritis: study protocol for a randomized controlled trial. *BMC.Musculoskelet.Disord., 14,* 266.

Ornetti, P., Parratte, S., Gossec, L., Tavernier, C., Argenson, J. N., Roos, E. M. et al. (2008). Cross-cultural adaptation and validation of the French version of the Knee injury and Osteoarthritis Outcome Score (KOOS) in knee osteoarthritis patients. *Osteoarthritis.Cartilage., 16,* 423-428.

Ottenbacher, K. & York, J. (1984). Strategies for evaluating clinical change: implications for practice and research. *American Journal of Occupational Therapy, 38,* 647-659.

Pereira, D., Peleteiro, B., Araujo, J., Branco, J., Santos, R. A., & Ramos, E. (2011). The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis.Cartilage., 19,* 1270-1285.

Ratzlaff, C. R., Koehoorn, M., Cibere, J., & Kopec, J. A. (2012). Is lifelong knee joint force from work, home, and sport related to knee osteoarthritis? *Int.J.Rheumatol., 2012,* 584193.

Rhon, D. (2008). Re: Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137-62. *Osteoarthritis.Cartilage., 16,* 1585.

Roach, H. I., Aigner, T., Soder, S., Haag, J., & Welkerling, H. (2007). Pathobiology of osteoarthritis: pathomechanisms and potential therapeutic targets. *Curr.Drug Targets., 8,* 271-282.

Rogind, H., Bibow-Nielsen, B., Jensen, B., Moller, H. C., Frimodt-Moller, H., & Bliddal, H. (1998). The effects of a physical training program on patients with osteoarthritis of the knees. *Archives of Physical Medicine and Rehabilitation, 79,* 1421-1427.

Roos, E. M. & Lohmander, L. S. (2003). The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual.Life Outcomes., 1,* 64.

Roos, E. M., Roos, H. P., Ekdahl, C., & Lohmander, L. S. (1998). Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scandinavian Journal of Medicine and Science in Sports, 8,* 439-448.

Roos, E. M., Roos, H. P., Lohmander, L. S., Ekdahl, C., & Beynnon, B. D. (1998). Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *Journal of Orthopaedic and Sports Physical Therapy, 28,* 88-96.

Schaible, H. G. (2012). Mechanisms of chronic pain in osteoarthritis. *Curr.Rheumatol.Rep., 14,* 549-556.

Schaible, H. G., Schmelz, M., & Tegeder, I. (2006). Pathophysiology and treatment of pain in joint disease. *Adv.Drug Deliv.Rev., 58,* 323-342.

Scholz, J. & Woolf, C. J. (2002). Can we conquer pain? *Nature Neuroscience, 5 Suppl,* 1062-1067.

Sharma, L., Dunlop, D. D., Cahue, S., Song, J., & Hayes, K. W. (2003). Quadriceps strength and osteoarthritis progression in malaligned and lax knees. *Annals of Internal Medicine, 138,* 613-619.

Singh, J. A., Dohm, M., & Borkhoff, C. (2013). Total joint replacement surgery versus conservative care for knee osteoarthritis and other non-traumatic diseases (protocol). *Cochrane Database of Systematic Reviews*.

Sofat, N., Ejindu, V., & Kiely, P. (2011). What makes osteoarthritis painful? The evidence for local and central pain processing. *Rheumatology.(Oxford), 50,* 2157-2165.

Somers, T. J., Keefe, F. J., Godiwala, N., & Hoyler, G. H. (2009). Psychosocial factors and the pain experience of osteoarthritis patients: new findings and new directions. *Current Opinion in Rheumatology, 21,* 501-506.

Sovani, S. & Grogan, S. P. (2013). Osteoarthritis: detection, pathophysiology, and current/future treatment strategies. *Orthop.Nurs., 32,* 25-36.

Staud, R. (2011). Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. *Curr.Rheumatol.Rep., 13,* 513-520.

Stemberger, R. & Kerschan-Schindl, K. (2013). Osteoarthritis: physical medicine and rehabilitation--nonpharmacological management. *Wiener Medizinische Wochenschrift, 163,* 228-235.

Sun, H. B. (2010). Mechanical loading, cartilage degradation, and arthritis. *Annals of the New York Academy of Sciences, 1211,* 37-50.

Suri, S., Gill, S. E., Massena de, C. S., Wilson, D., McWilliams, D. F., & Walsh, D. A. (2007). Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Annals of the Rheumatic Diseases, 66,* 1423-1428.

Turk, D. C. & Melzack, R. (2011). *Handbook of pain assessment*. (vols. 3rd ed.) New York: Guilford Press.

Valdes, A. M. & Spector, T. D. (2009). The contribution of genes to osteoarthritis. *Medical Clinics of North America, 93,* 45-66, x.

van Saase, J. L., van Romunde, L. K., Cats, A., Vandenbroucke, J. P., & Valkenburg, H. A. (1989). Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Annals of the Rheumatic Diseases, 48,* 271-280.

Visser, A. W., de, M. R., le, C. S., den, H. M., Rosendaal, F. R., & Kloppenburg, M. (2014). The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Annals of the Rheumatic Diseases*.

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M. et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380,* 2163-2196.

Wang, S. Y., Olson-Kellogg, B., Shamliyan, T. A., Choi, J. Y., Ramakrishnan, R., & Kane, R. L. (2012). Physical therapy interventions for knee pain secondary to osteoarthritis: a systematic review. *Annals of Internal Medicine, 157,* 632-644.

Williams, D. A., Gendreau, M., Hufford, M. R., Groner, K., Gracely, R. H., & Clauw, D. J. (2004). Pain assessment in patients with fibromyalgia syndrome: a consideration of methods for clinical trials. *Clinical Journal of Pain, 20,* 348-356.

Wise, B. L., Niu, J., Zhang, Y., Wang, N., Jordan, J. M., Choy, E. et al. (2010). Psychological factors and their relation to osteoarthritis pain. *Osteoarthritis.Cartilage., 18,* 883-887.

Wolery, M. & Harris, S. R. (1982). Interpreting results of single-subject research designs. *Physical Therapy, 62,* 445-452.

Woolf, C. J. (2004). Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine, 140,* 441-451.

Woolf, C. J. & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science, 288,* 1765-1769.

Wu, C. W., Morrell, M. R., Heinze, E., Concoff, A. L., Wollaston, S. J., Arnold, E. L. et al. (2005). Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. *Seminars in Arthritis and Rheumatism, 35,* 197-201.

Zhang, W., Moskowitz, R. W., Nuki, G., Abramson, S., Altman, R. D., Arden, N. et al. (2007). OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis.Cartilage., 15,* 981-1000.

Zhang, W., Nuki, G., Moskowitz, R. W., Abramson, S., Altman, R. D., Arden, N. K. et al. (2010). OARSI recommendations for the management of hip and knee

osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis.Cartilage., 18,* 476-499.

Zhang, Y., Nevitt, M., Niu, J., Lewis, C., Torner, J., Guermazi, A. et al. (2011). Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis and Rheumatism, 63,* 691-699.

Tables

Figures

Acronyms and definitions

BMI	Body mass index
KOOS	Knee injury and Osteoarthritis Outcome Score
MCID	Minimal clinical importance difference
MDC	Minimal detectable change
NRS	Numeric Rating Scale
Pain fluctuation	Variation of pain from lowest to highest measured with either KOOS pain or NRS for pain.
Pain intensity	Level of pain measured with KOOS pain or NRS for pain

Appendix

Appendix 1: Questionnaires used in this study

Appendix 2: Ethical committee approval scheme

Appendix 3: Subjects approval scheme

Appendix 4: Complete results from the KOOS pain and the NRS for pain presented graphically

Appendix 5: Results from the KOOS pain and the NRS for pain presented by numbers

Appendix 6: Fluctuations in the KOOS pain and the NRS for pain presented by numbers

Appendix 1: Questionnaires used in this study

Baseline – Dato

P1. Hvor ofte har du vondt i kneet?
Aldri Månedlig Ukentlig Daglig Hele tiden

Hvilken grad av smerte har du hatt i kneet ditt det siste døgnet ved følgende aktiviteter?

P2. Snu/vende på belastet kne
Ingen Lett Moderat Betydelig Svært stor

P3. Rette kneet helt ut
Ingen Lett Moderat Betydelig Svært stor

P4. Bøye kneet helt
Ingen Lett Moderat Betydelig Svært stor

P5. Gå på flatt underlag
Ingen Lett Moderat Betydelig Svært stor

P6. Gå opp eller ned trapper
Ingen Lett Moderat Betydelig Svært stor

P7. Om natten i sengen (smerter som forstyrrer søvnen)
Ingen Lett Moderat Betydelig Svært stor

P8. Sittende eller liggende
Ingen Lett Moderat Betydelig Svært stor

P9. Stående
Ingen Lett Moderat Betydelig Svært stor

På en skala fra null til ti, hvor null representerer ”ingen smerte” mens ti representerer ”verst tenkelige smerte”:

N1. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært på det høyeste?
N2. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært på det laveste?
N3. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært i gjennomsnitt?

Intervensjonsuke – Dato

P1. Hvor ofte har du vondt i kneet?
Aldri Månedlig Ukentlig Daglig Hele tiden

Hvilken grad av smerte har du hatt i kneet ditt den siste uken ved følgende aktiviteter?

P2. Snu/vende på belastet kne
Ingen Lett Moderat Betydelig Svært stor

P3. Rette kneet helt ut
Ingen Lett Moderat Betydelig Svært stor

P4. Bøye kneet helt
Ingen Lett Moderat Betydelig Svært stor

P5. Gå på flatt underlag
Ingen Lett Moderat Betydelig Svært stor

P6. Gå opp eller ned trapper
Ingen Lett Moderat Betydelig Svært stor

P7. Om natten i sengen (smerter som forstyrrer søvnen)
Ingen Lett Moderat Betydelig Svært stor

P8. Sittende eller liggende
Ingen Lett Moderat Betydelig Svært stor

P9. Stående
Ingen Lett Moderat Betydelig Svært stor

På en skala fra null til ti, hvor null representerer ”ingen smerte” mens ti representerer ”verst tenkelige smerte”:

N1. I løpet av siste uke, hvor smertefullt har dine knesmerter vært på det høyeste?
N2. I løpet av siste uke, hvor smertefullt har dine knesmerter vært på det laveste?
N3. I løpet av siste uke, hvor smertefullt har dine knesmerter vært i gjennomsnitt?

Post intervention – Dato

P1. Hvor ofte har du vondt i kneet?
Aldri Månedlig Ukentlig Daglig Hele tiden

Hvilken grad av smerte har du hatt i kneet ditt det siste døgnet ved følgende aktiviteter?

P2. Snu/vende på belastet kne
Ingen Lett Moderat Betydelig Svært stor

P3. Rette kneet helt ut
Ingen Lett Moderat Betydelig Svært stor

P4. Bøye kneet helt
Ingen Lett Moderat Betydelig Svært stor

P5. Gå på flatt underlag
Ingen Lett Moderat Betydelig Svært stor

P6. Gå opp eller ned trapper
Ingen Lett Moderat Betydelig Svært stor

P7. Om natten i sengen (smerter som forstyrrer søvnen)
Ingen Lett Moderat Betydelig Svært stor

P8. Sittende eller liggende
Ingen Lett Moderat Betydelig Svært stor

P9. Stående
Ingen Lett Moderat Betydelig Svært stor

På en skala fra null til ti, hvor null representerer ”ingen smerte” mens ti representerer ”verst tenkelige smerte”:

N1. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært på det høyeste?
N2. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært på det laveste?
N3. I løpet av siste døgn, hvor smertefullt har dine knesmerter vært i gjennomsnitt?

Appendix 2: Ethical committee approval scheme

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	08.07.2014	2012/334/REK sør-øst C
			Deres dato:	Deres referanse:
			25.06.2014	

Vår referanse må oppgis ved alle henvendelser

Britt Elin Øiestad
Oslo universitetssykehus HF

2012/334 Kneleddsartrose og trening

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Britt Elin Øiestad

Vi viser til søknad om prosjektendring datert 25.06.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst C på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
I innsendt skjema beskrives følgende endringer:

-Innhenting av nye data fra samme utvalgsgrupper:

Det ønskes å innhente nye data fra samme utvalgsgrupper med samme deltakere som før, der en masterstudent skal samle inn ny informasjon om knesmerte for å undersøke smertevariasjon.

Komitéen har ingen forskningsetiske innvendinger til prosjektet slik det nå foreligger.

Vedtak
Komitéen har vurdert endringsmeldingen og godkjenner prosjektet slik det nå foreligger med hjemmel i helseforskningslovens § 11. Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren.

Komiteens vedtak kan påklages, jf. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Britt Ingjerd Nesheim
prof. dr. med
leder REK sør-øst C

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

Appendix 3: Subjects approval scheme

Oslo universitetssykehus

NAR

Forespørsel om deltakelse i forskningsprosjektet

"Smertevariasjon hos pasienter med kneleddsartrose – En kohortestudie"

Bakgrunn og hensikt
Dette er en forespørsel til deg som allerede deltar i forskningsstudien "Effekt av styrke- og utholdenhetstrening på fysisk funksjon og bruskhelse hos pasienter med kneleddsartrose – En randomisert kontrollert studie". Du forespørres om å delta i en liten tilleggsstudie som er knyttet opp til den studien du allerede deltar i. Formålet med denne tilleggstudien er å se hvordan smerte forandrer seg over tid hos pasienter med kneleddsartrose.

Hva innebærer studien?
Studien innebærer at du skal svare på tolv spørsmål angående dine knesmerter. Tiden det tar for å besvare disse spørsmålene er under fem minutter. Du har valget mellom å besvare spørsmålene enten via telefon eller e-post. Disse 12 spørsmålene vil du besvare daglig i 7 dager før du begynner med treningen i hovedstudien du allerede deltar i. Underveis mens du trener i hovedstudien vil du besvare de 12 spørsmålene en gang i uken. Etter at du er ferdig med treningen i hovedstudien vil vi videre be deg besvare spørsmålene daglig i 7 dager. Deltagelse i denne tilleggstudien har ingen innvirkning på din deltagelse i hovedstudien som du allerede deltar i.

Mulige fordeler og ulemper
Du vil få en grundig kartlegging av dine knesmerter. Spørsmålene du besvarer er utviklet basert på topp internasjonal kunnskap. Din deltagelse i studien vil bidra til å øke kunnskapen om hvordan smerte varier blant pasienter med kneleddsartrose.

Hva skjer med informasjonen om deg?
Data som innhentes på kneet ditt vil lagres i manuelle arkiv med personidentifikasjon som låses inn, og du har til enhver tid full innsynsrett i dataene. Elektronisk lagres dataene kun med nummer. Lagringen av data vil foregå i henhold til personopplysningsloven.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Etisk komité har vurdert prosjektet.

Prosjektet planlegges avsluttet når vi har rekruttert 20 deltagere. Dersom nye studier basert på innsamlende opplysninger blir aktuelle, ber vi om tillatelse til å henvende oss til deg for nytt samtykke for slik bruk. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din deltagelse i hovedstudien eller for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige deltagelse eller behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte prosjektansvarlig Joakim Ordahl på tlf 98883310.

Med vennlig hilsen

Joakim M. Ordahl
Prosjektansvarlig
Masterstudent i idrettsfysioterapi ved Norges idrettsshøgskole

Rett til innsyn og sletting av opplysninger om deg
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Forsikring
Du har de samme rettighetene og forsikringsvilkårene som du ville hatt dersom du ikke deltok i denne undersøkelsen.

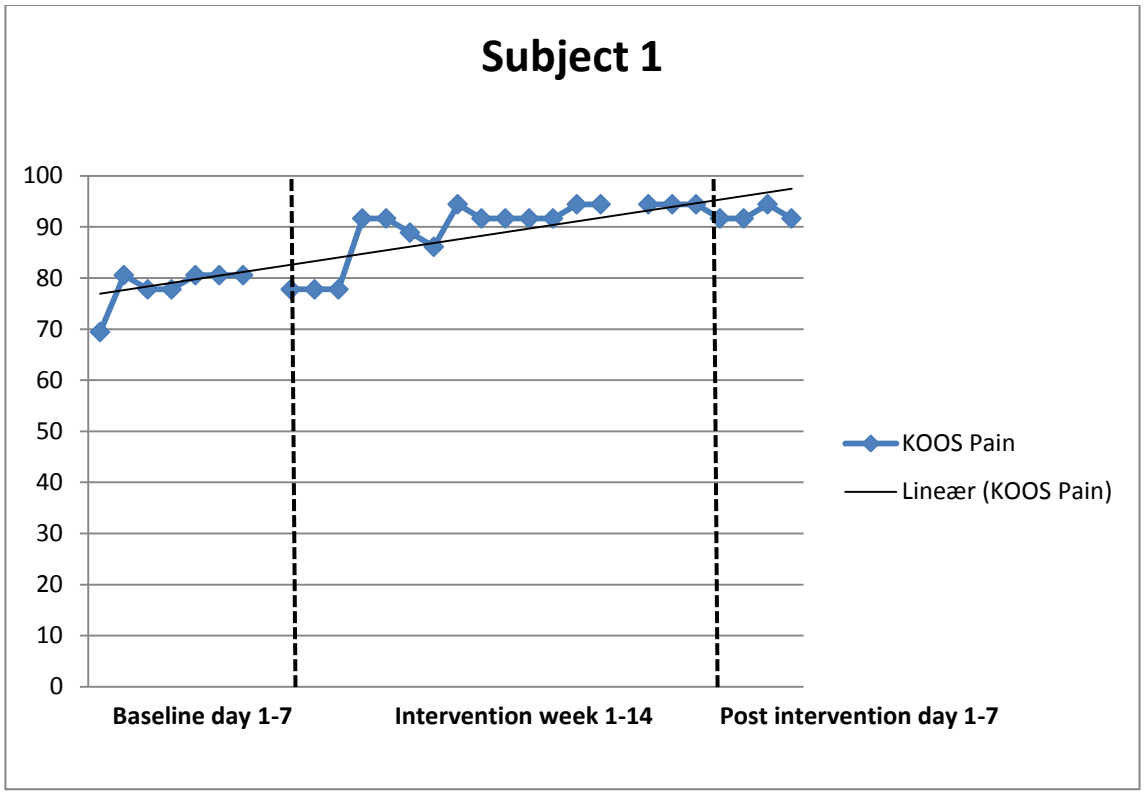
Samtykke til deltakelse i studien

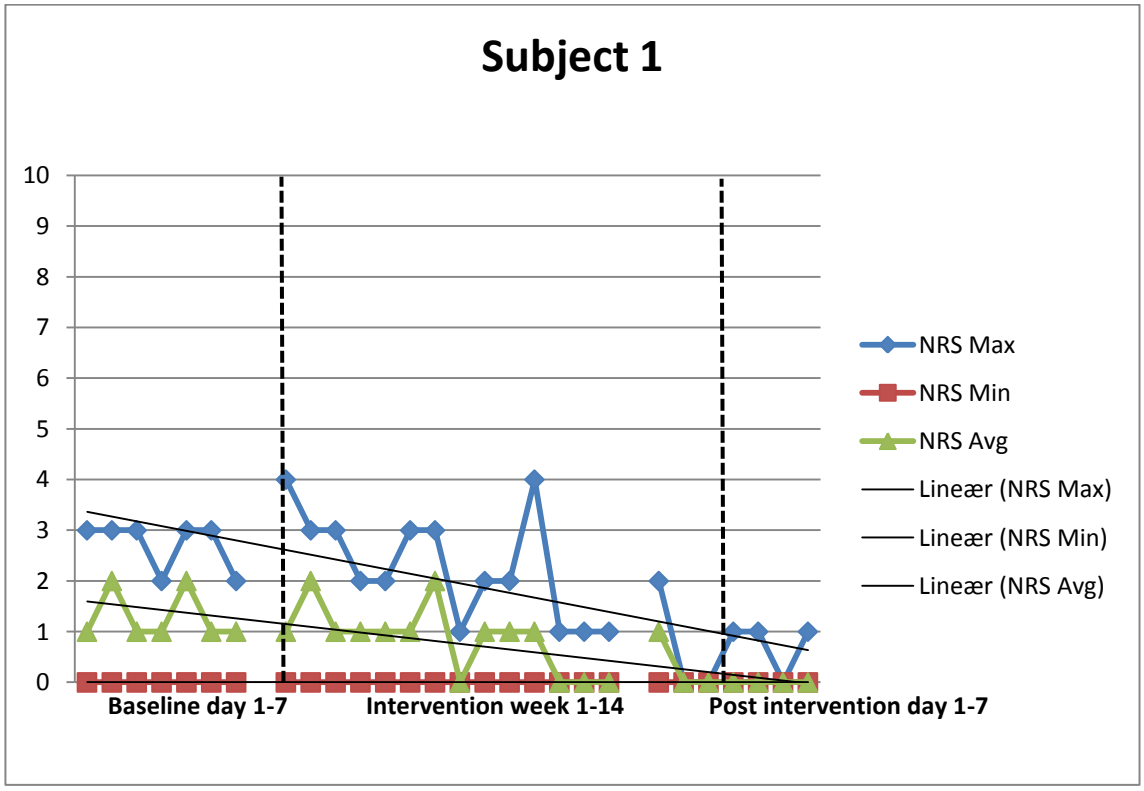
Jeg er villig til å delta i studien ☐

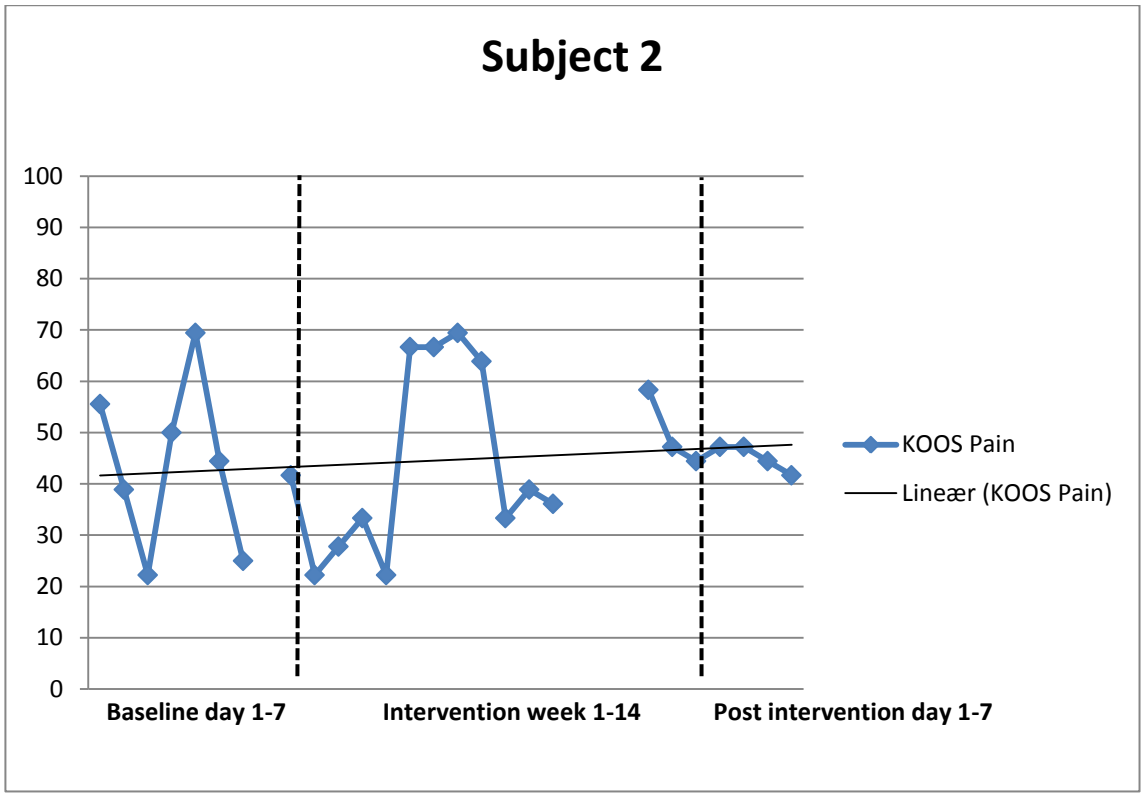
(Signert av prosjektdeltaker, dato)

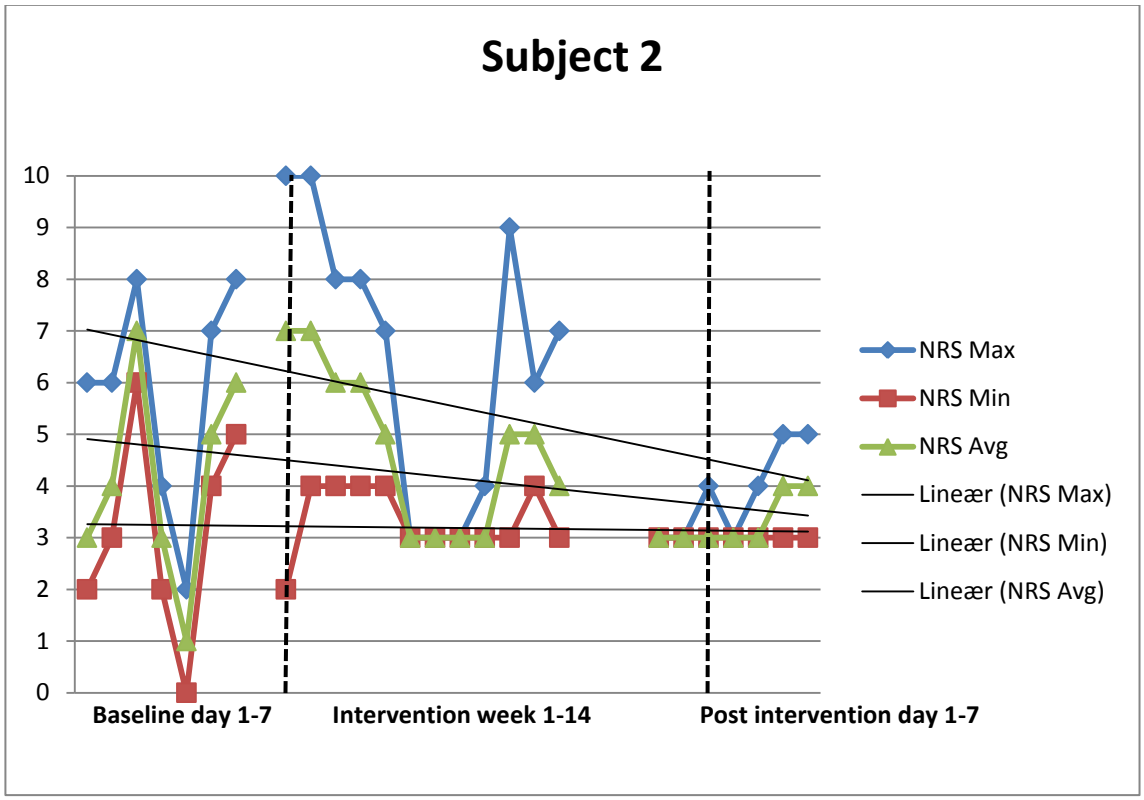
(Signert av prosjektansvarlig om at informasjon er gitt, dato)

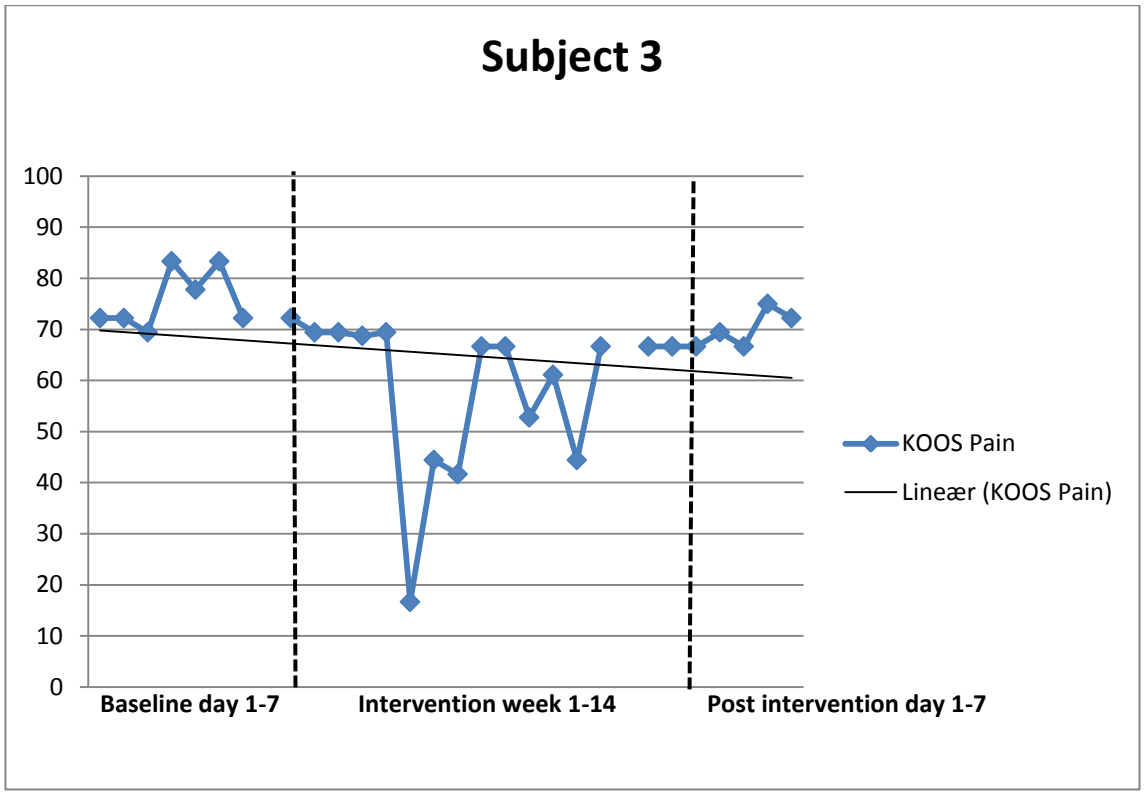
Appendix 4: Complete results from the KOOS pain and the NRS for pain presented graphically

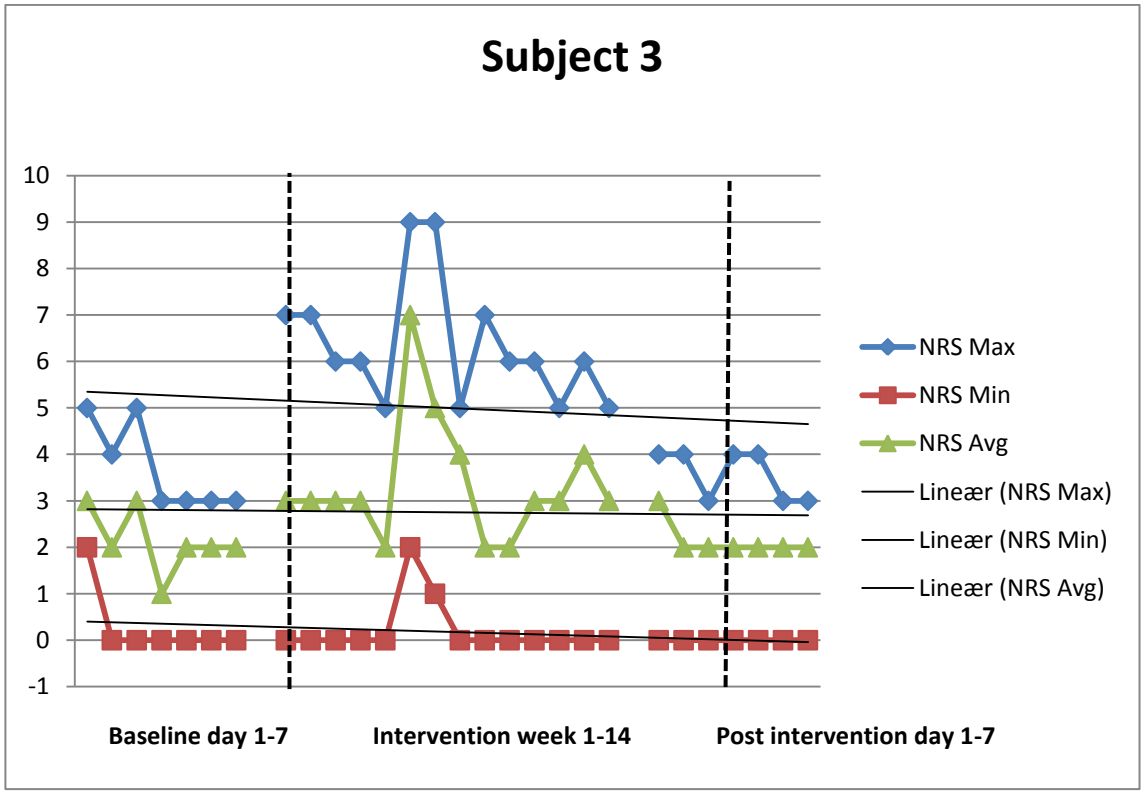


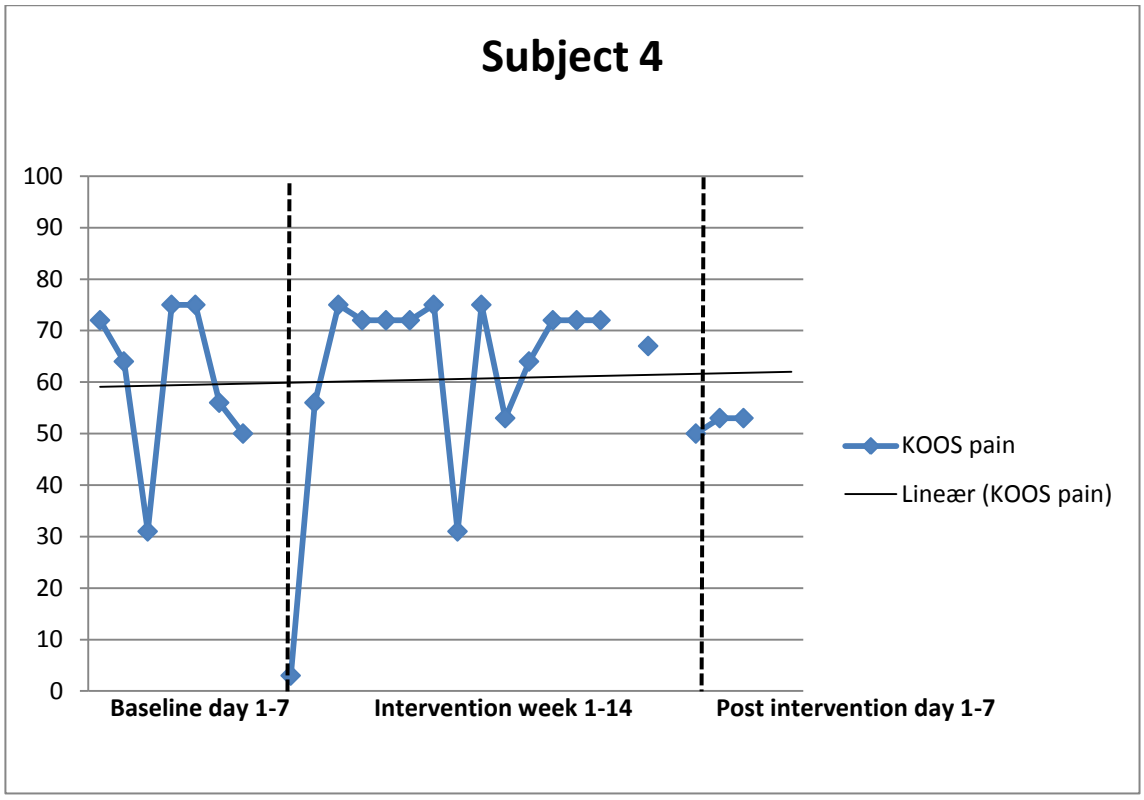


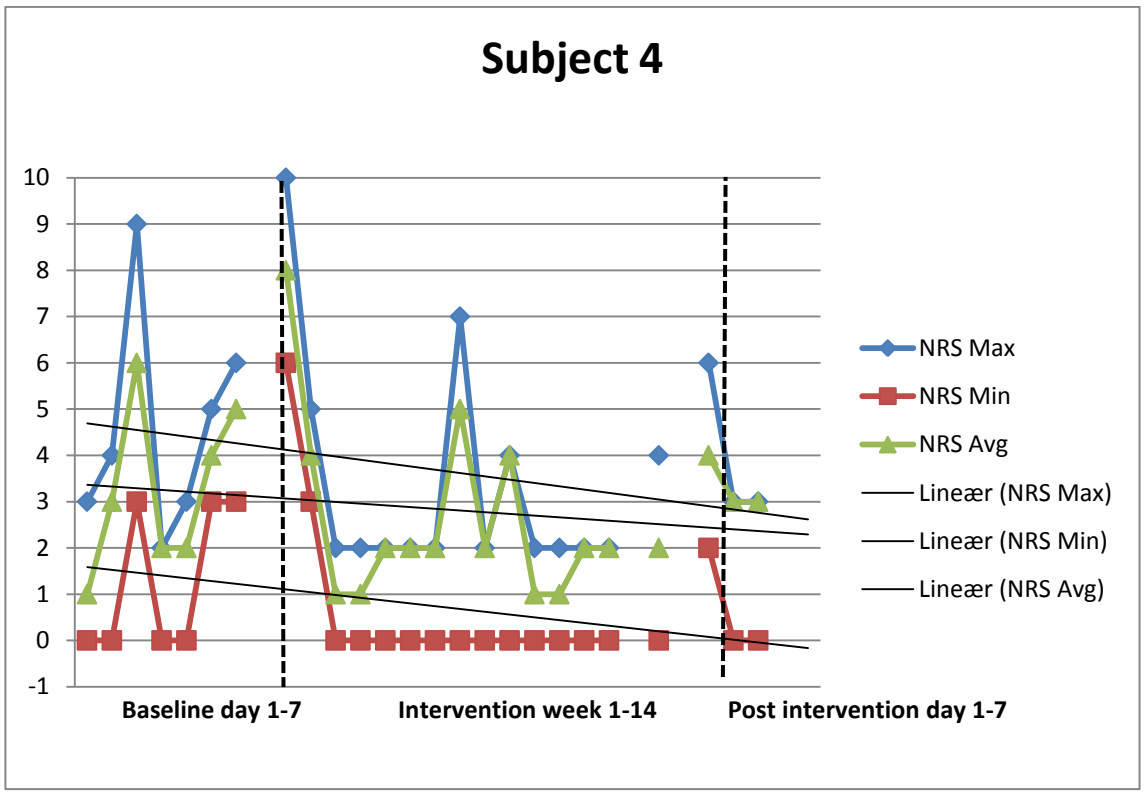

Subject 2
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

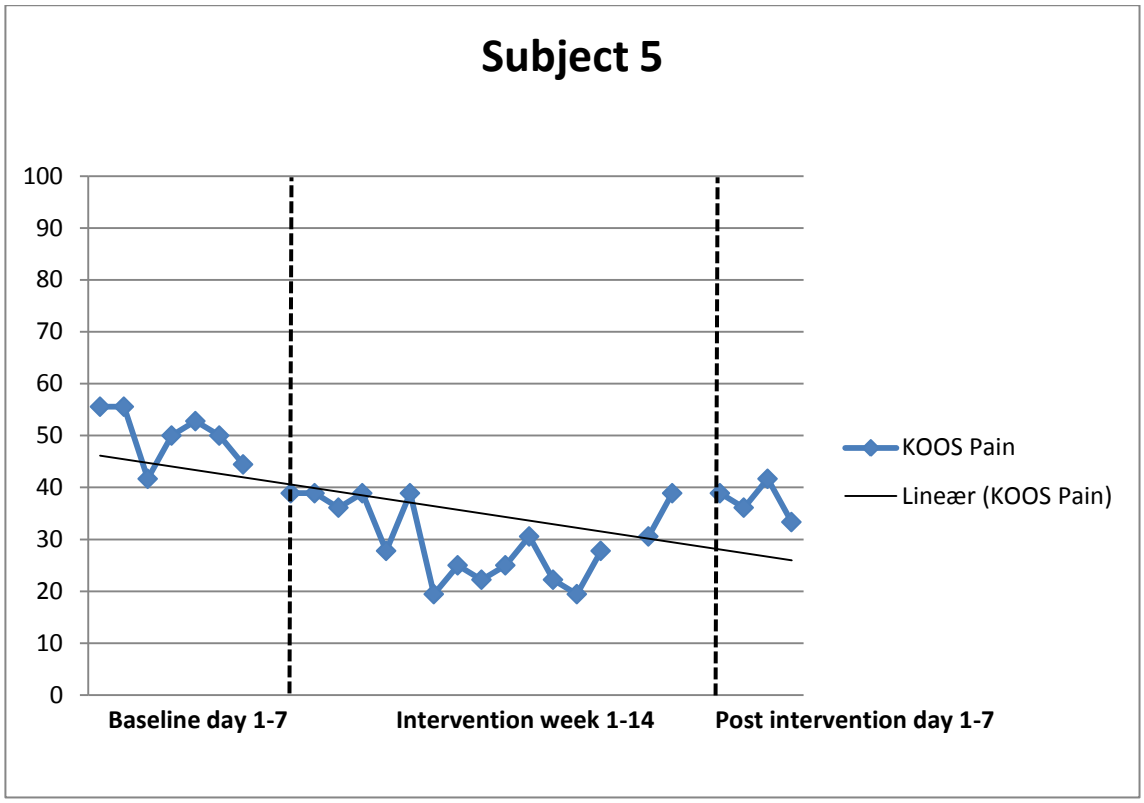

Subject 2
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

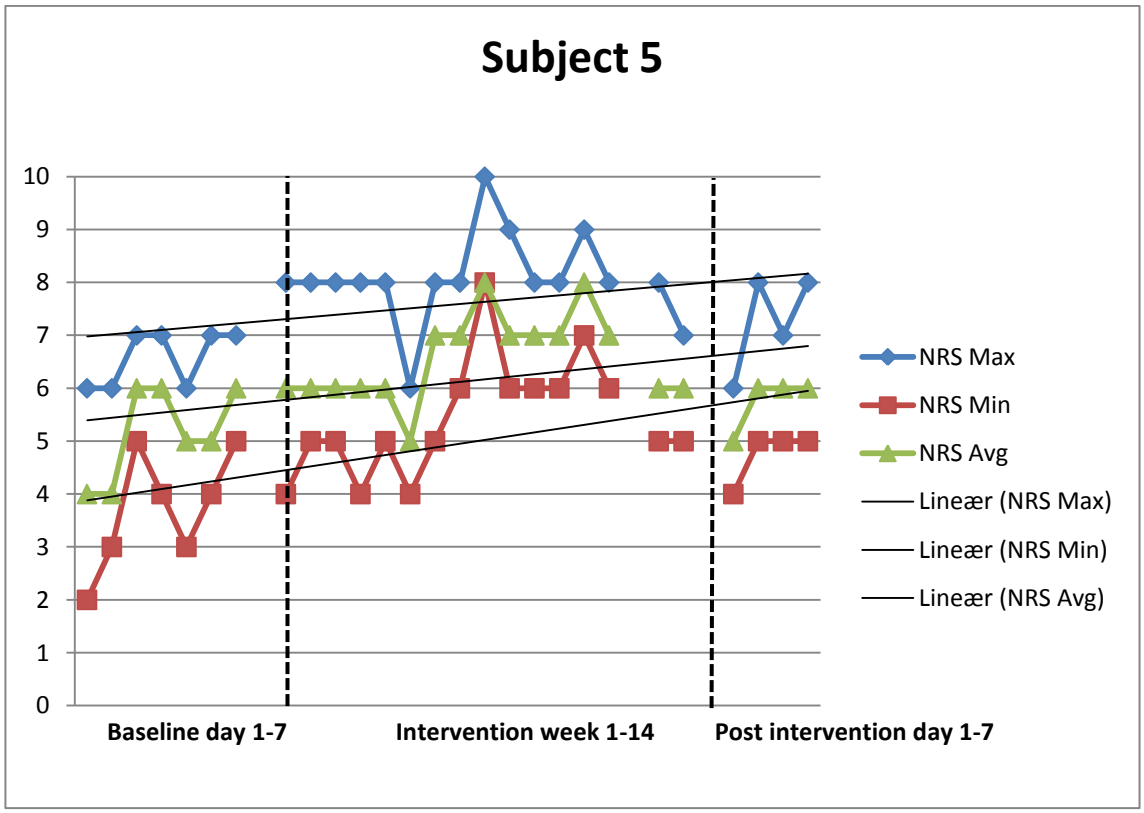

Subject 3
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

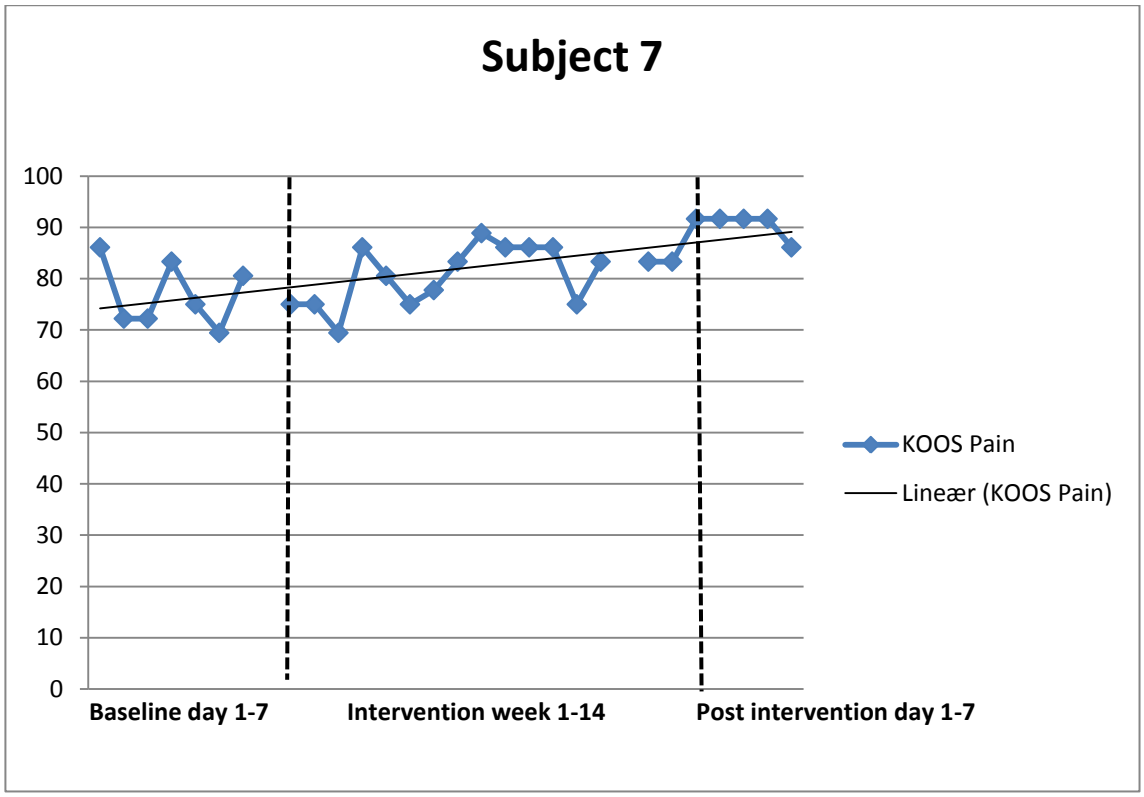

Subject 3
10
9
8
7
6
5
4
3
2
1
0
-1
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

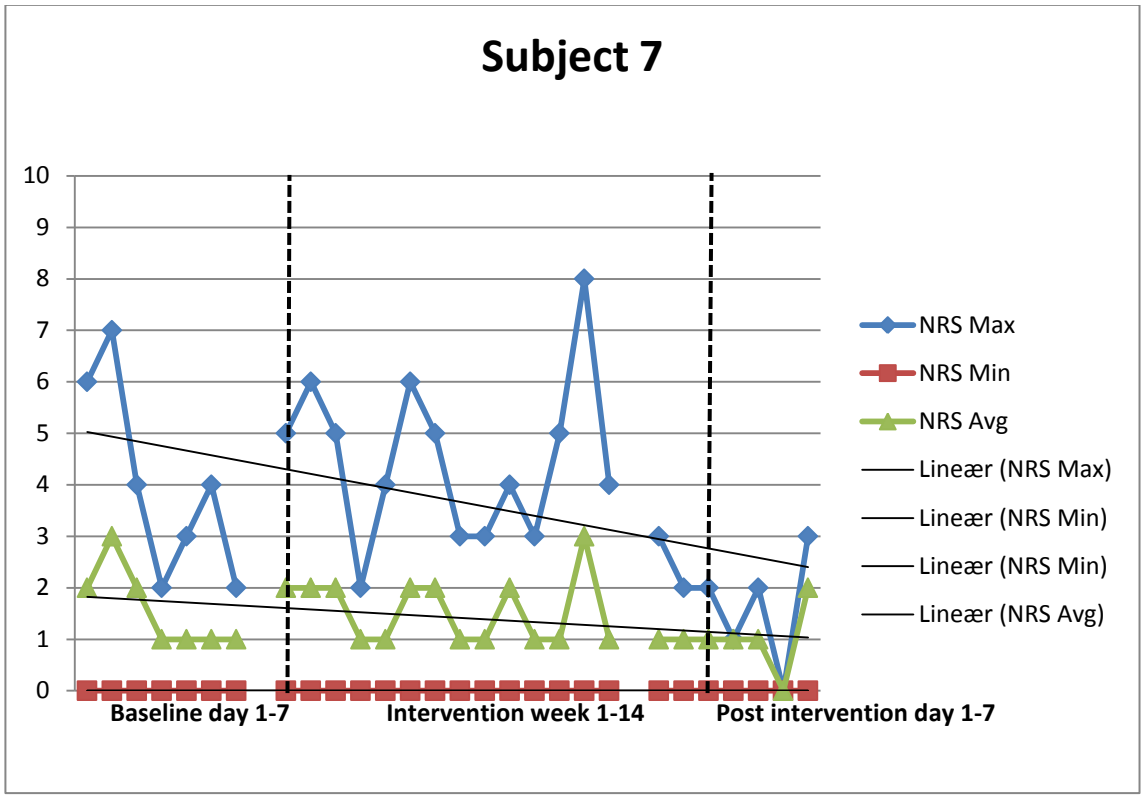

Subject 4
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS pain
Lineær (KOOS pain)

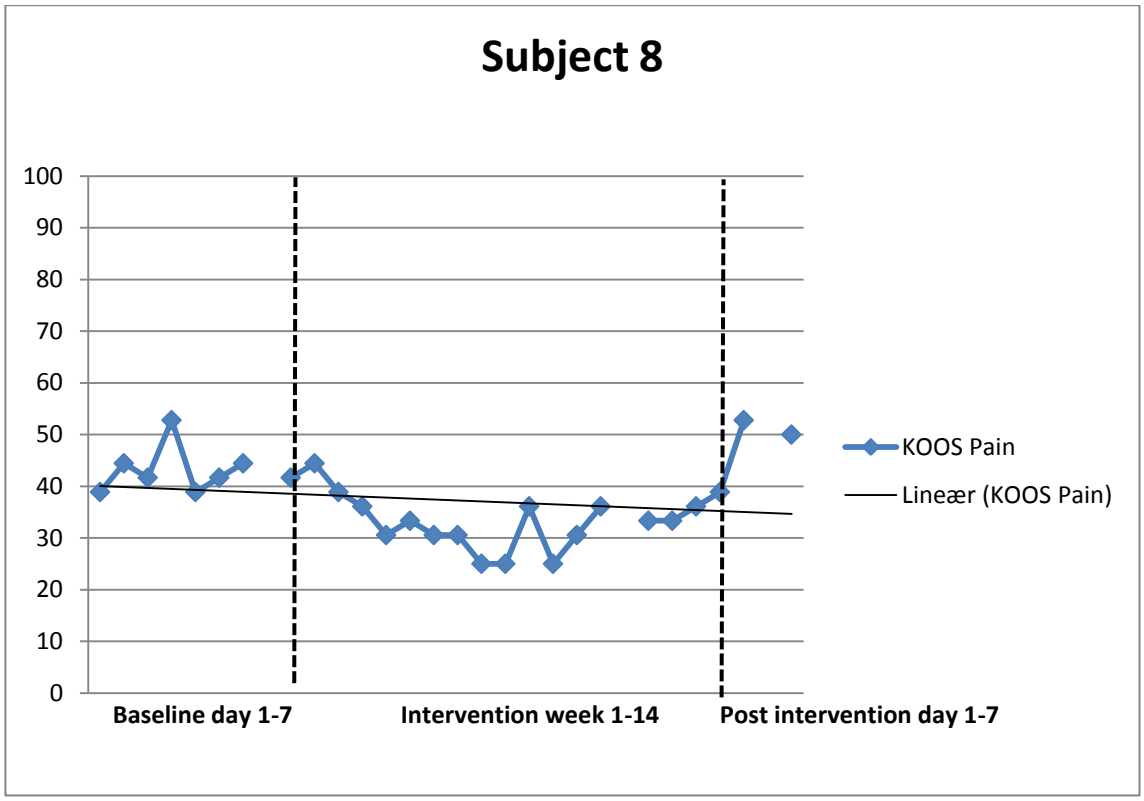

Subject 4
10
9
8
7
6
5
4
3
2
1
0
-1
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

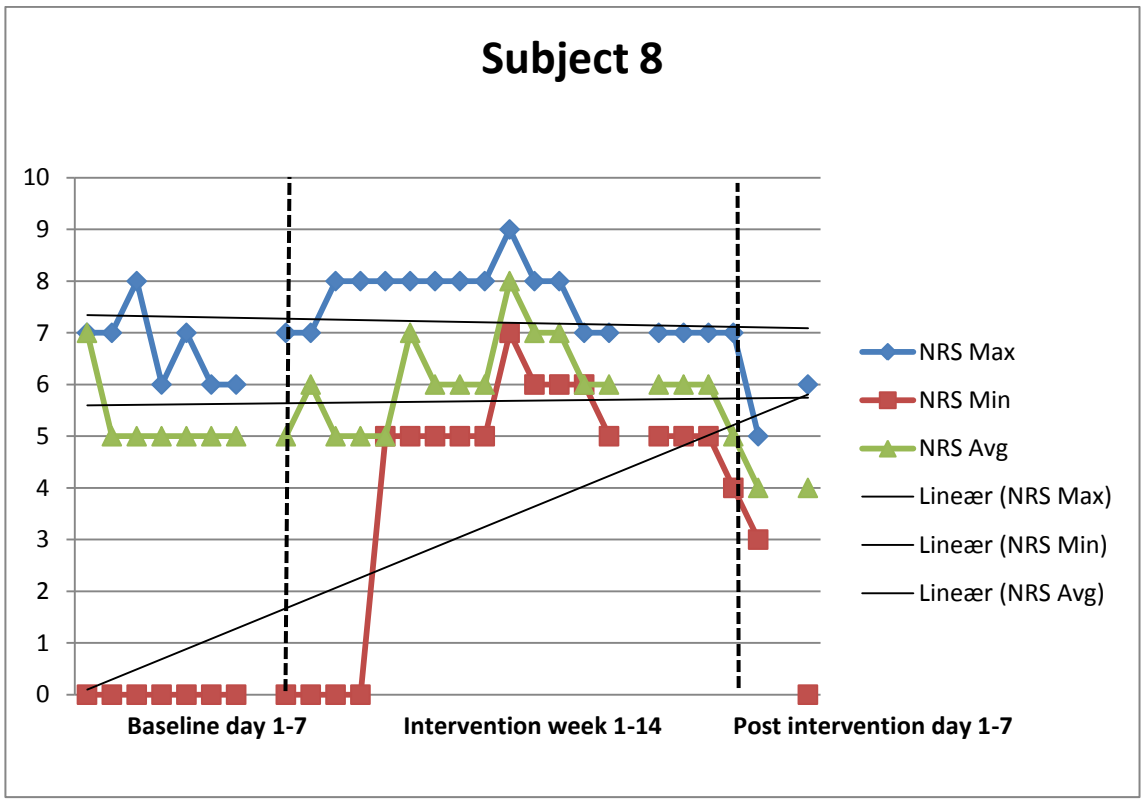

Subject 5
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

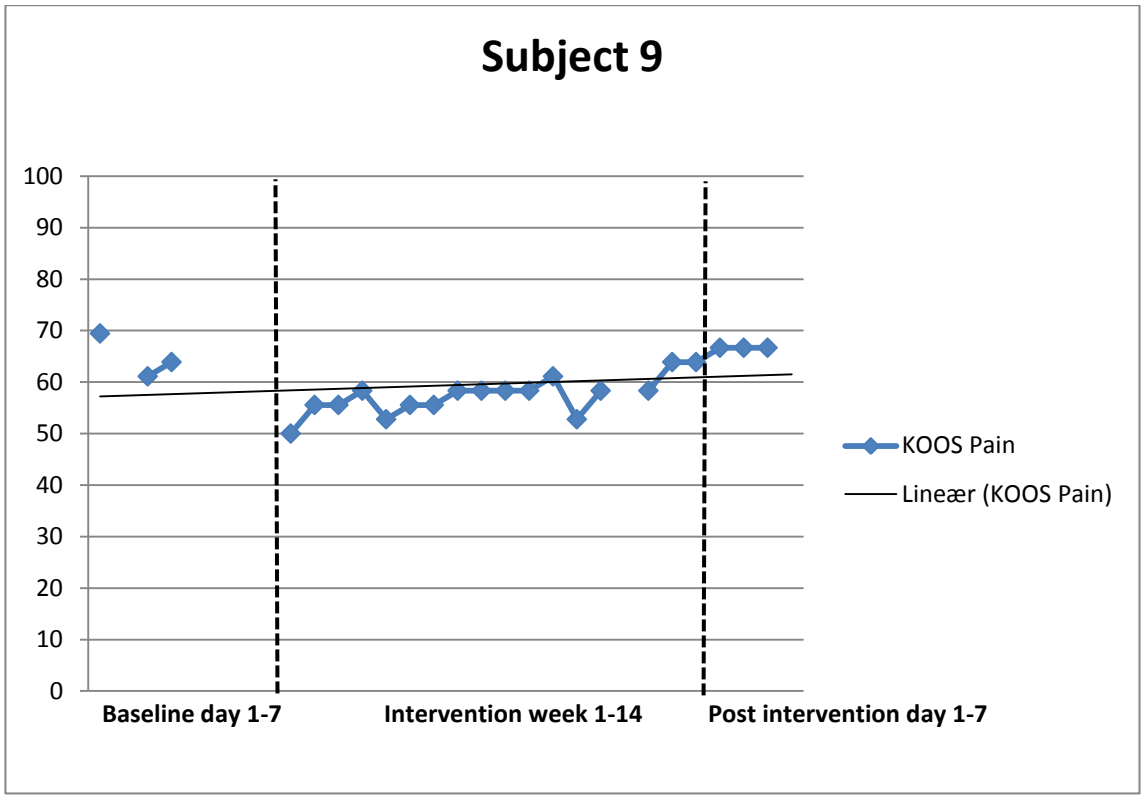

Subject 5
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

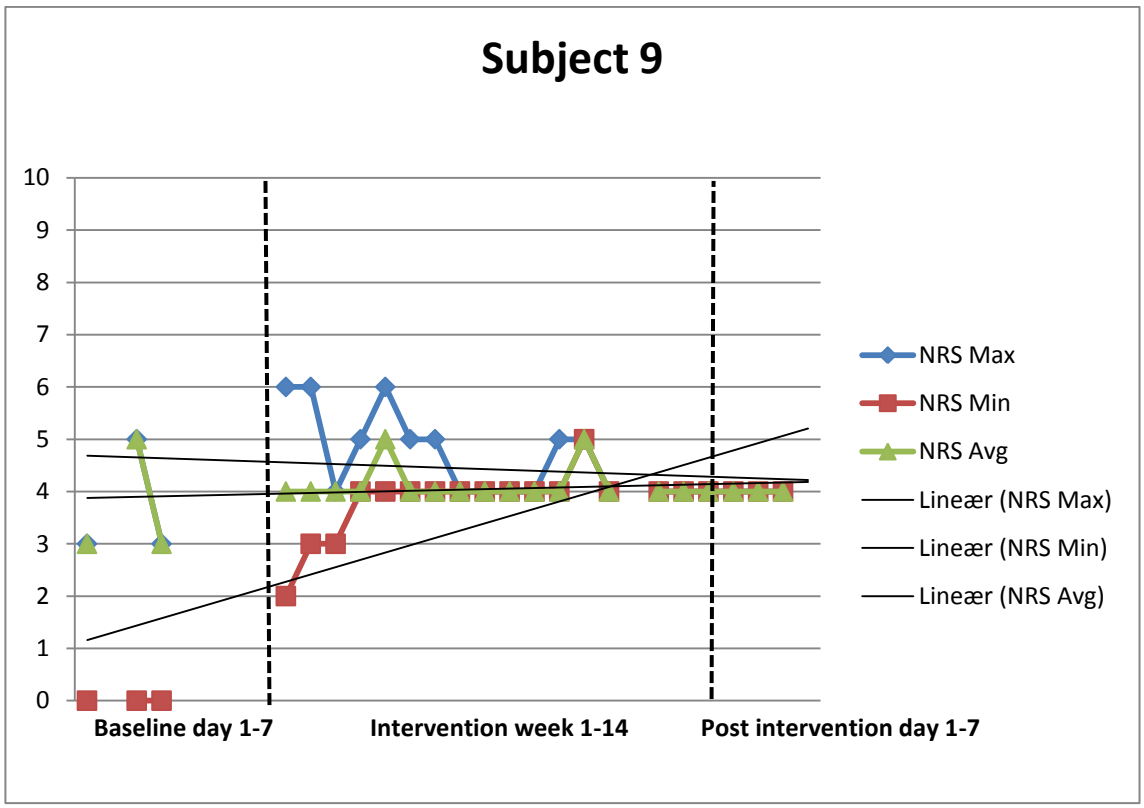

Subject 7
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

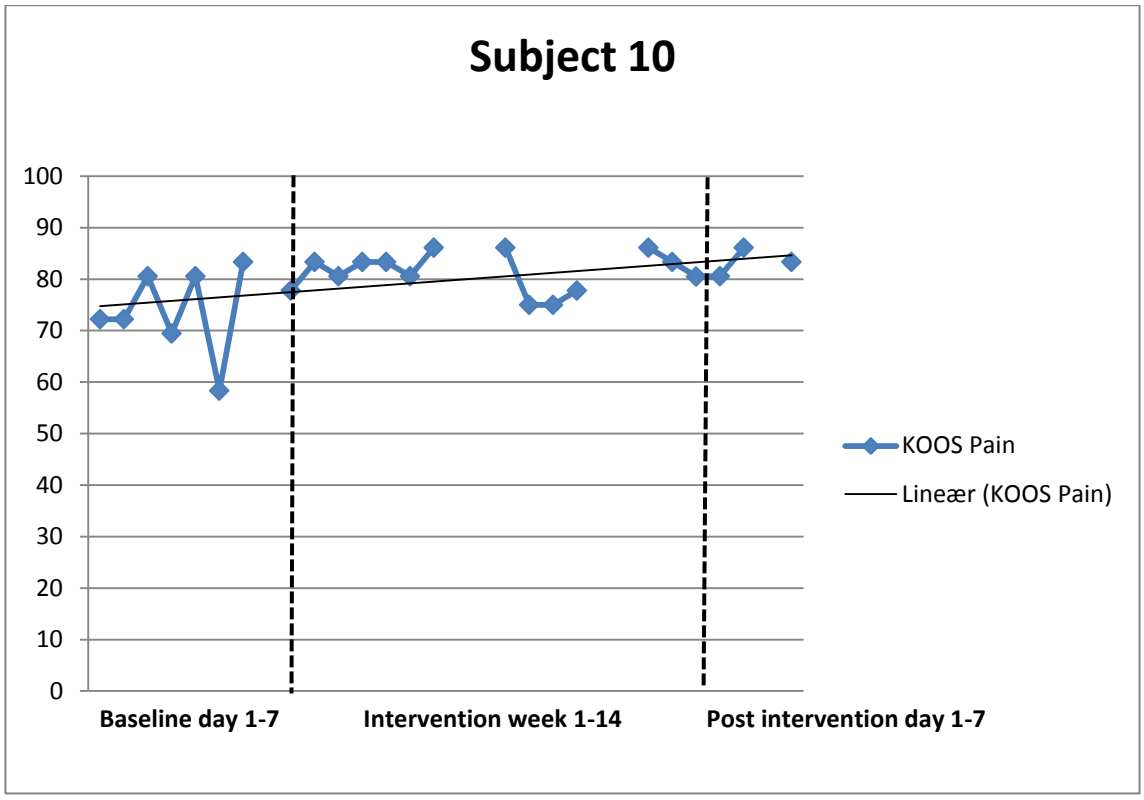

Subject 7
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Min)
Lineær (NRS Avg)

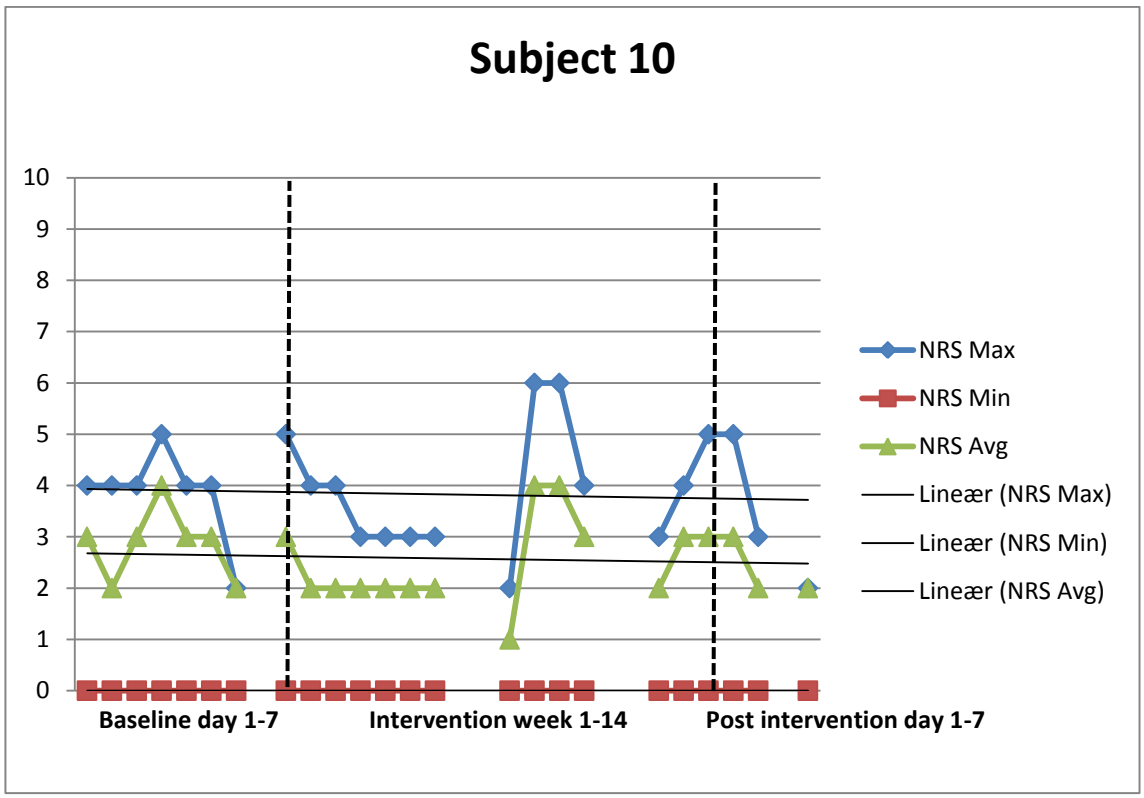

Subject 8
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

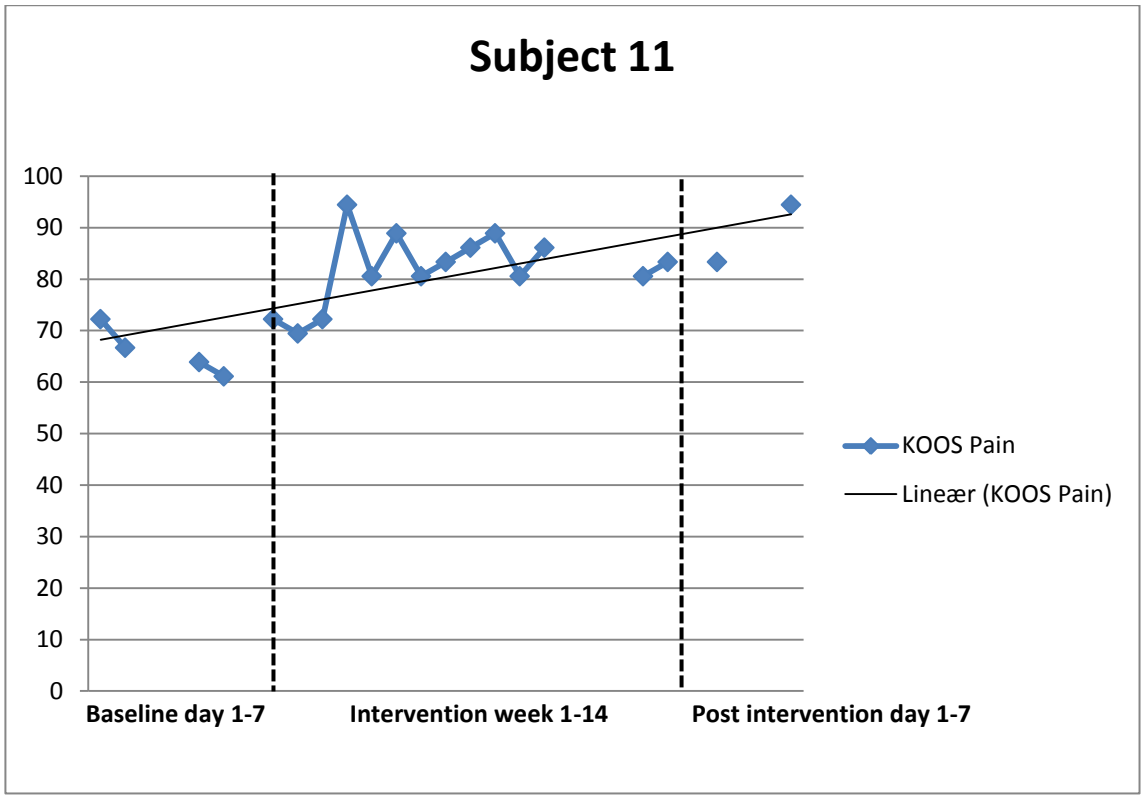

Subject 8
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

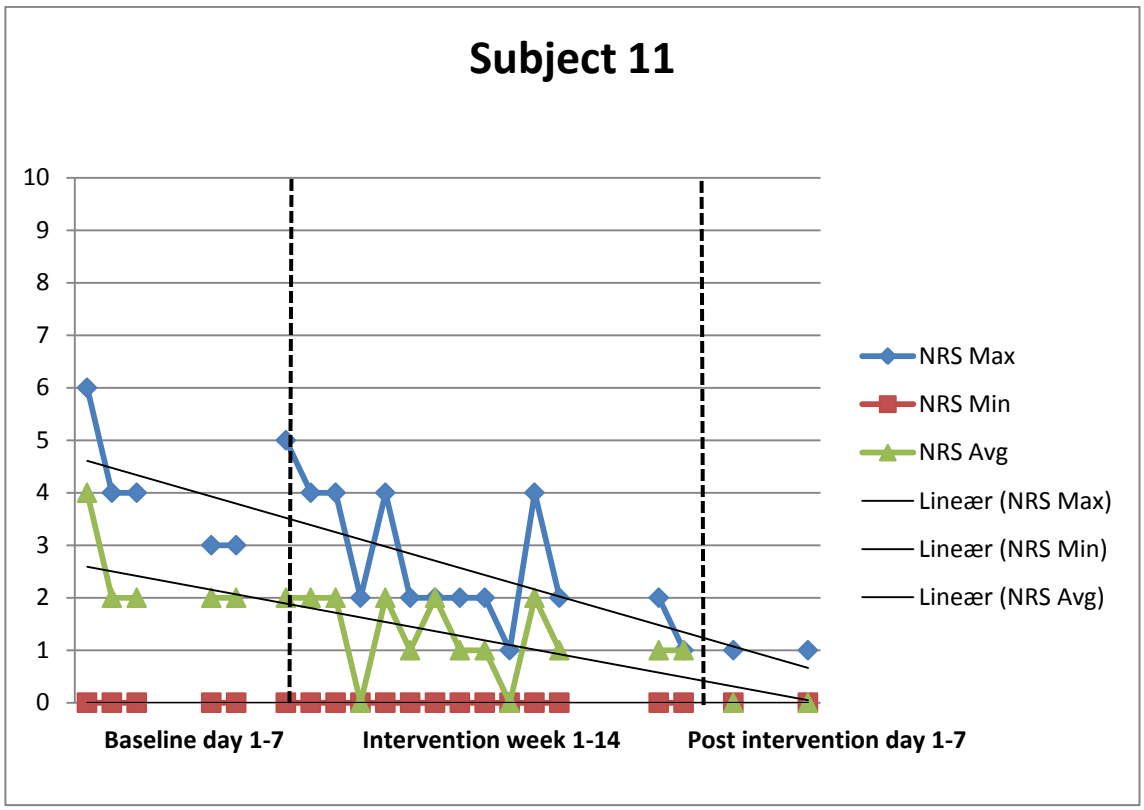

Subject 9
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)

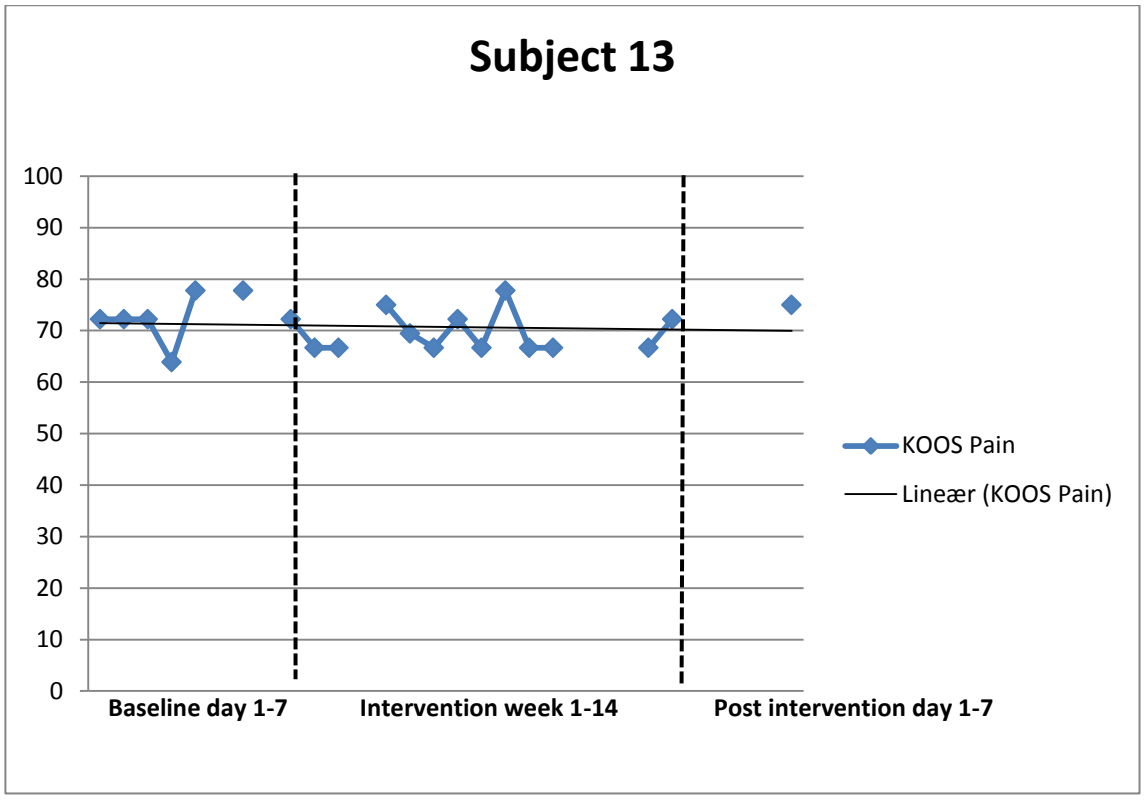

Subject 9
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

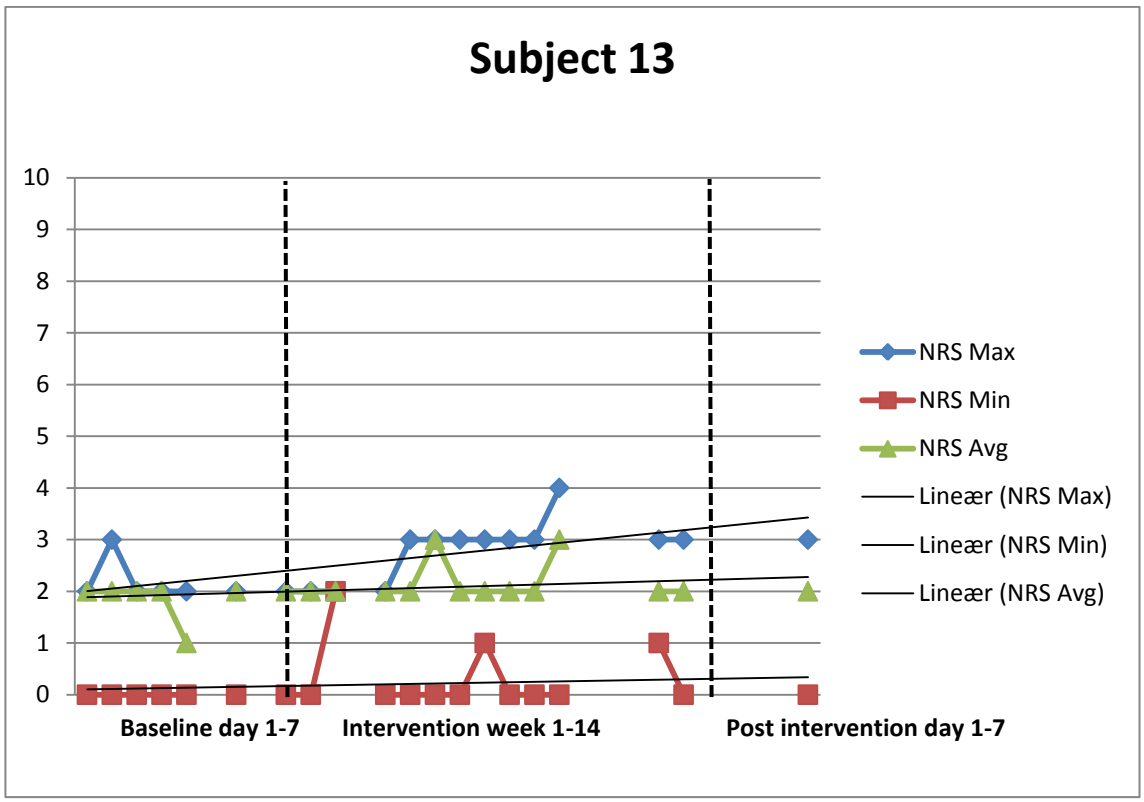

Subject 10
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)


Subject 10
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)


Subject 11
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)


Subject 11
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)


Subject 13
100
90
80
70
60
50
40
30
20
10
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
KOOS Pain
Lineær (KOOS Pain)


Subject 13
10
9
8
7
6
5
4
3
2
1
0
Baseline day 1-7
Intervention week 1-14
Post intervention day 1-7
NRS Max
NRS Min
NRS Avg
Lineær (NRS Max)
Lineær (NRS Min)
Lineær (NRS Avg)

Appendix 5: *Results for KOOS pain and NRS presented by numbers*

The table summarizes maximum, minimum, and average scores for KOOS pain and NRS for pain at baseline, intervention, and post intervention.

Subject	1	2	3	4	5	7	8	9	10	11	13
KOOS pain maximum baseline	81	69	83	75	56	86	53	69	83	72	78
KOOS pain minimum baseline	69	22	69	31	42	69	39	61	58	61	64
KOOS pain average baseline	78	44	76	60	50	77	43	65	74	67	73
KOOS pain maximum intervention	94	69	72	75	39	89	44	61	86	94	78
KOOS pain minimum intervention	78	22	17	3	19	69	25	50	75	69	67
KOOS pain average intervention	89	44	58	62	29	81	33	56	81	82	70
KOOS pain maximum post intervention	94	58	75	67	42	92	53	67	86	94	75
KOOS pain minimum post intervention	92	42	67	50	31	83	33	58	81	81	67
KOOS pain average post intervention	93	47	69	56	37	88	41	64	83	85	71
NRS maximum baseline	3	8	5	9	7	7	8	5	5	6	3
NRS minimum baseline	0	0	0	0	2	0	0	0	0	0	0
NRS average baseline	1,3	4,1	2,1	3,3	5,1	1,6	5,3	3,7	2,9	2,4	1,8
NRS maximum intervention	4	10	9	10	10	8	9	6	6	5	4
NRS minimum intervention	0	2	0	0	4	0	0	2	0	0	0
NRS average intervention	0,9	4,8	3,4	2,6	6,6	1,6	6,1	4,1	2,5	1,3	2,2
NRS maximum post intervention	2	5	4	6	8	3	7	4	5	2	3
NRS minimum post intervention	0	3	0	0	4	0	0	4	0	0	0
NRS average post intervention	0,1	3,3	2,1	3	5,8	1	5,2	4	2,5	0,5	2

Appendix 6: *Fluctuations in KOOS pain and NRS for pain presented by numbers.*
The table summarizes the difference between the highest and lowest score (fluctuation) for each subject during baseline, intervention, and post intervention.

Subject	1	2	3	4	5	7	8	9	10	11	13	μ	Min	Max
KOOS pain fluctuation baseline	12	47	14	44	14	17	14	8	25	11	14	20	8	44
NRS fluctuation baseline	3	8	5	9	5	7	8	5	6	5	3	6	3	9
KOOS pain fluctuation intervention	16	47	55	72	20	20	19	11	11	25	11	28	11	72
NRS fluctuation intervention	4	8	9	10	6	8	9	4	6	5	4	7	4	10
KOOS pain fluctuation post intervention	2	16	8	17	11	9	20	9	5	13	8	11	2	20
NRS fluctuation post intervention	2	2	4	6	4	3	3	0	5	2	3	3	0	6