

# BMJ Open How does exercise dose affect patients with long-term osteoarthritis of the knee? A study protocol of a randomised controlled trial in Sweden and Norway: the SWENOR Study

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## ABSTRACT

**Introduction** Osteoarthritis (OA) of the knee is characterised by knee pain, disability and degenerative changes, and places a burden on societies all over the world. Exercise therapy is an often-used modality, but there is little evidence of what type of exercise dose is the most effective, indicating a need for controlled studies of the effect of different dosages. Thus, the aim of the study described in this protocol is to evaluate the effects of high-dose versus low-dose medical exercise therapy (MET) in patients with knee OA.

**Methods and analysis** This is a multicentre prospective randomised two-arm trial with blinded assessment and data analysis. We are planning to include 200 patients aged 45–85 years with symptomatic (pain and decreased functioning) and X-ray verified diagnosis of knee OA. Those eligible for participation will be randomly allocated to either high-dose (n=100) or low-dose (n=100) MET. All patients receive three supervised treatments each week for 12 weeks, giving a total of 36 MET sessions. The high-dose group exercises for 70–90 min compared with 20–30 min for the low-dose group. The high-dose group exercises for a longer time, and receives a greater number of exercises with more repetitions and sets. Background and outcome variables are recorded at inclusion, and outcome measures are collected after every sixth treatment, at the end of treatment, and at 6-month and 12-month follow-ups. Primary outcome is self-rated knee functioning and pain using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The primary end point is at the end of treatment after 3 months, and secondary end points are at 6 months and 12 months after the end of treatment.

**Ethics and dissemination** This project has been approved by the Regional Research Ethics Committees in Stockholm, Sweden, and in Norway. Our results will be submitted to peer-reviewed journals and presented at national and international conferences.

**Trial registration number** NCT02024126; Pre-results.

## BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and is a major health problem worldwide, causing illness and disability.<sup>1 2</sup> The burden to society caused by knee OA is

## Strengths and limitations of this study

- To the best of our knowledge, this is the first multicentre study, with a biopsychosocial view of pain, prospectively comparing the effectiveness of two defined doses of pain-free or close to pain-free exercise therapies in patients with symptomatic knee osteoarthritis.
- The proposed project includes a relatively large sample where outcomes are evaluated both during the 12-week intervention period, at the end of treatment, and at 6 months and 12 months, respectively.
- The overall project uses both subjective and objective data, and includes analyses of cost-effectiveness and early predictors for a follow-up clinical outcome.
- Even though the different components of the exercise programmes are well described, one limitation could be possible confounders related to the exercise dose given.

substantial.<sup>3</sup> The knee joint is most frequently affected, which commonly results in chronic joint pain, knee stiffness, decreased functioning, reduced quality of life (QoL) and sick leave.<sup>4</sup> The associated costs of OA are estimated to range between 1% and 2.5% of the gross national product as calculated in six industrialised countries (Sweden, Australia, Canada, France, UK and USA).<sup>5</sup>

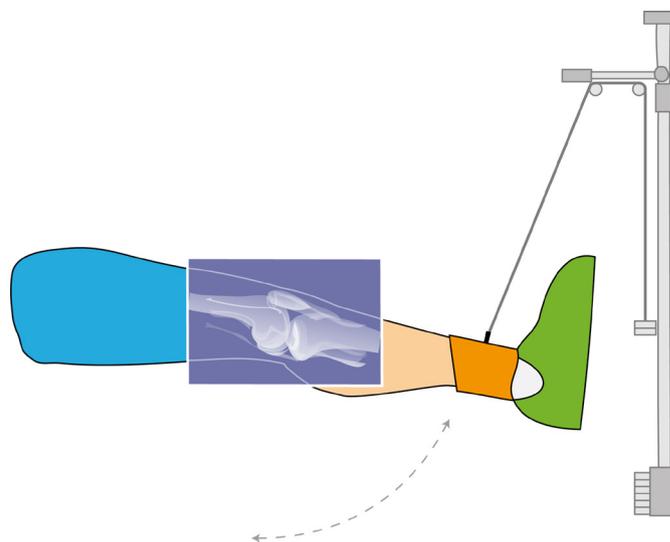
Traditionally, knee OA has been defined as a pathological condition characterised by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and subchondral bone sclerosis) and thickening of the capsule.<sup>6</sup> The mechanisms of knee OA-related pain are, however complex,<sup>7</sup> particularly in chronic pain conditions where pain experience is nowadays believed to be more a result of changes in the nervous system than in tissue

structures,<sup>8</sup> that is, peripheral and central sensitisation.<sup>9</sup> This may partly explain why there are poor correlations between structural degenerative changes of the knee, and pain and functioning.<sup>10 11</sup>

In a systematic review, it was concluded that there exists high-level evidence that land-based therapeutic exercise provides short-term effects on pain relief, and that there is a moderate quality evidence regarding improvement in physical functioning among patients with knee OA.<sup>12</sup> Despite this, several questions remain unanswered, particularly regarding dose, intensity and duration of the exercise therapy applied.<sup>13</sup> These unanswered questions may be one of the reasons why we see a large variation in treatment effects observed across studies making it difficult to conclude what is the optimal dose when delivering exercise therapy.<sup>12 13</sup> The exercises vary from neuromuscular exercise,<sup>14</sup> knee joint stabilisation exercises,<sup>15</sup> strengthening exercises<sup>16</sup> and endurance exercises.<sup>17</sup> These forms of exercise therapy do not necessarily take into consideration the theories of local and central sensitisation, thus opening up avenues for exercise therapies where the goal is modulation of pain, decreasing local and central sensitisations. The knowledge that pain and swelling inhibits motor output, decreases range of motion (ROM) and changes coordination,<sup>18</sup> and that a strengthening exercise programme can cause adverse effects,<sup>19</sup> questions the use of strengthening exercises. In their review,<sup>19</sup> Liu *et al* concluded that out of 121 trials, 53 had no comments about adverse events, 25 reported no adverse events and 43 reported adverse events. The majority of the adverse events from the strength training were muscle strain and joint pain, while more adverse events were reported when performing high-intensity strength training. In this context there is increasing evidence<sup>20</sup> that exercise therapy should focus more on treating pain-related knee OA such as peripheral and central sensitisation<sup>8</sup> and pain-related bodily and psychological changes<sup>21</sup> from a biopsychosocial perspective<sup>22 23</sup> rather than an impairment like muscle strength. This view is supported by research showing that pain-related fear is more disabling than pain itself.<sup>24</sup> To break the vicious circle of long-term knee pain, we believe it is important to see beyond the knee,<sup>8</sup> beyond an impairment such as muscle strength,<sup>25</sup> using a biopsychosocial sensitisation model of pain.<sup>23</sup>

### Medical exercise therapy

Medical exercise therapy (MET) focuses on applying optimal dose of exercise, that is, combining global aerobic exercises with semiglobal and local joint exercises, where the goal is to apply 70–90 min of active dynamic exercise therapy.<sup>26–35</sup> Using the principle of self-paced exercises<sup>36</sup> the patient is to perform more than a 1000 pain-free or close to pain-free repetitions per MET session.<sup>26–35</sup> Even though the optimal dose goal of MET is high, the treatment usually starts with a low dose lasting 15–20 min mirroring the ability of the patient within a biopsychosocial context,<sup>22 23</sup> starting with an acceptable baseline where the patient manages the exercise therapy.<sup>23 26</sup>



**Figure 1** The principle of deloading, performing local knee exercise.

Global exercise activates the whole body exercising the trunk as well as upper and lower extremities; semiglobal exercise activates muscles, joints and other structures in the extremity; and local exercise activates one joint and the muscles acting on it. Sessions of global exercises are performed several times during one treatment occasion, where the goal is to substantially increase the heart rate activating the endocrine and pain modulating systems of the body, that is, the descending pain-inhibiting system, achieving cortical and spinal inhibition of nociceptive input. Semiglobal and local exercises are performed for the same purpose, however, they are performed in sets of three where each set consists of 30 repetitions. Local exercise can also be performed continuously for 3–5 min as one set, for example, deloaded knee extension, see figure 1.

To achieve a high volume of pain-free or close to pain-free repetitions, the principle of deloading is applied where the weight stack from a pulley apparatus is used to deload a part of the body or the whole body, resulting in less joint forces in the knee joint, see figure 1.

The theoretical basis for the principle of deloading is that the weight from the pulley deloads the weight of the lower leg with a decrease in the compressive forces between bony and cartilaginous structures. Deloading also results in decreased pulling and loading of muscles, tendons and other soft tissues, decreasing sensitisation including mechanical/loading allodynia, making it possible to exercise pain-free or close to pain-free.

MET has been evaluated in several clinical trials, and has been shown to be effective, both in the short term and the long term, in patients with long-term low back pain with or without sciatica,<sup>37</sup> subacromial pain<sup>33–35</sup> and long-term anterior knee pain.<sup>27 28</sup> In these latter studies, an exercise dose lasting 70–90 min has been more favourable than an exercise dose lasting 20–30 min. In a narrative review, Lorås *et al*, 2015,<sup>23</sup> included four Randomised Controlled Trials (RCTs) on the effectiveness of

high-dose MET, concluding that high-dose MET was positive and promising. However, to be able to draw any firm conclusions about the efficacy in patients with knee OA, rigorous trials are needed on the effect of MET in this major patient group.<sup>38</sup>

Effect trials of cost-effectiveness are also needed as they are presently lacking in the scientific literature, and the present project has the potential to fill this knowledge gap. It is also important to point out that no exercise protocol is suited to all patients, and as knowledge of early predictors of poor treatment outcomes obtained from longitudinal data is sparse, the development of patient-customised treatments is hindered.<sup>39</sup> According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) as well as a recent review,<sup>40</sup> prediction studies are needed to be able to better individualise the treatment and match the most promising treatment option to a certain patient profile in order to maximise treatment outcomes and minimise costs. Therefore, we plan to conduct a RCT post hoc prediction study to gain insights into which patient characteristics predict treatment outcome and which patients benefit more or less from exercise treatments.

In this trial, the rationale for comparing high-dose MET (70–90 min) versus low-dose MET (20–30 min) is that high-dose MET should be more effective through an increased activation of the pain modulation systems, like the descending pain inhibiting system.<sup>41</sup> The evidence is that exercise-induced hypoalgesia is obtained through higher and more intensive exercise doses of 70% of heart rate reserve (HRR), activating the pain modulating systems and decreasing the sensation of pain.<sup>42</sup> However, it has also been shown that an exercise intensity of 50% of HRR is capable of producing an analgesic effect in healthy adults,<sup>43</sup> with similar exercise intensities used in both high-dose and low-dose MET. This could have important implications for the use of exercise in the management of pain, particularly in deconditioned individuals (eg, older adults with OA of the knee). In 2008 it was shown for the first time that an endurance activity lasting 2 hours resulted in the production of endogenous neuropeptides (endorphins), creating chemical reactions in brain areas involved in cognitive function and pain modulation, primarily in the prefrontal cortices, insula and the limbic system.<sup>44</sup> The rationale is that high-dose MET exercising for 70–90 min may result in an increased production of endogenous neuropeptides in the spinal cord, the brain stem and in the brain, compared with a lower dose MET exercising 20–30 min. The hypothesis is that this should result in less pain and improved functioning in favour of the high-dose MET therapy.

## AIM OF THE STUDY

The aim of this project is to prospectively evaluate short-term and long-term effects of high-dose MET compared with low-dose MET in patients with X-ray verified knee

OA regarding pain, functioning and cost-effectiveness. A further aim is to conduct a post hoc analysis on early prognostic factors that predict short-term and long-term follow-up outcomes, by targeting patients' early status and patients' adherence to the intervention. The long-term goal is to further develop and implement updated knowledge into knee OA rehabilitation to meet the challenge of tomorrow's patients with knee OA pain.

This study seeks to answer the following research questions:

1. What is the effect of high-dose MET compared with a low-dose exercise therapy (low-dose MET) with respect to self-rated pain, functional limitations, health-related QoL, depression and anxiety?
2. What is the effect of high-dose MET compared with low-dose MET on objective performance measures such as physical functioning of a 20-metre walk, sit to stand and single knee bends, and pain threshold as determined by a PainMatcher instrument (Cefar Medical AB, Lund, Sweden)?
3. What is the cost-effectiveness of MET in patients with knee OA with respect to costs against potential effects (incremental cost-effectiveness ratio, ICER), and cost per quality-adjusted life year (QALY)?
4. Which patient characteristics (demographic or disease-related) predict long-term treatment outcomes with a focus on pain, functional limitation and health-related QoL? What important interaction effects between patient characteristics and exercise dose may predict treatment outcomes?

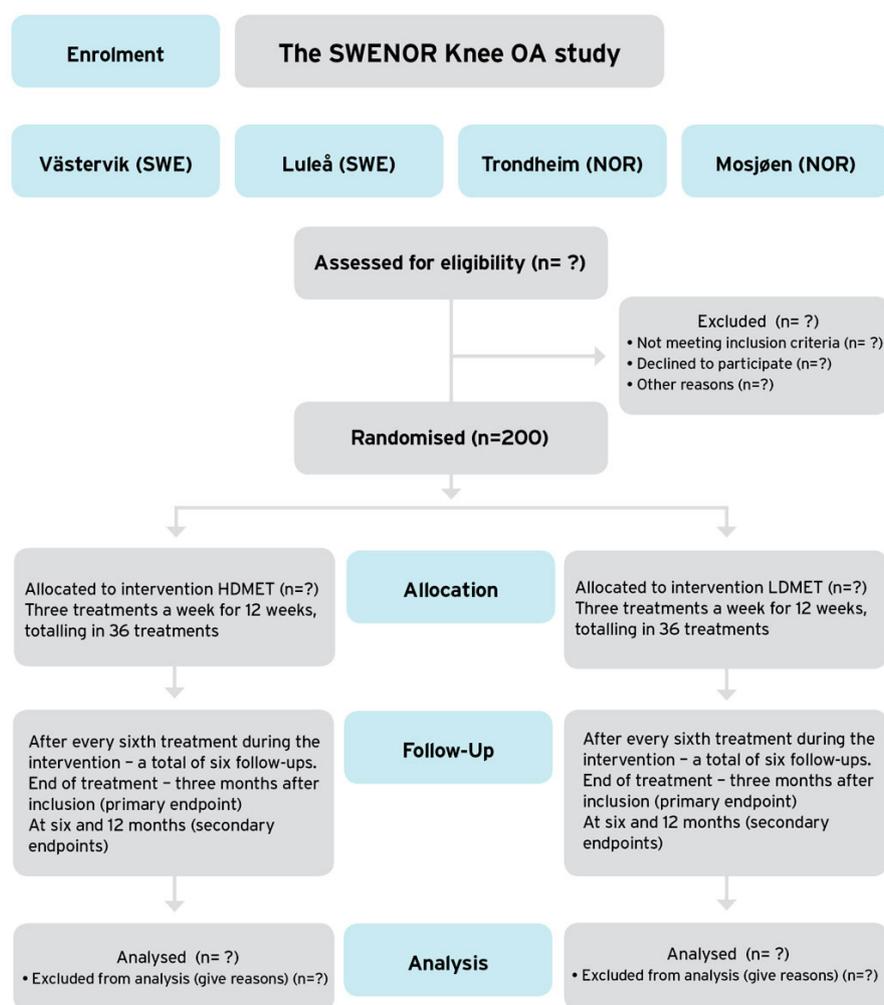
## MATERIAL AND METHODS

### Study design

This is a phase 3 superiority trial of high-dose versus low-dose MET. The trial is blinded regarding outcome assessment and analyses. It is a two-arm multicentre trial of a 12-week exercise intervention with a 12-month follow-up. Measurements will be taken at baseline and during the treatment at 2 weeks (6 treatments), 4 weeks (12 treatments), 6 weeks (18 treatments), 8 weeks (24 treatments), 10 weeks (30 treatments), 12 weeks (36 treatments), which is the end of the treatment, and at follow-ups at 26 weeks and 52 weeks after the end of the treatment. Primary end point is at the end of the treatment. Secondary end points are at the 26-week and 52-week follow-ups. The study will conform to Consolidated Standards of Reporting Trials guidelines for reporting parallel, randomised trials<sup>45</sup> (see figure 2).

### Participants

We are planning to include 200 patients with a diagnosis of symptomatic and radiographic knee OA who will be recruited from primary and secondary healthcare settings in Luleå and Västervik in Sweden, and in Trondheim and Mosjøen in Norway, named the SWENOR Knee OA Study.



**Figure 2** Flow chart of the design and run of the study. HDMET, high-dose MET; LDMET, low-dose MET; MET, medical exercise therapy; OA, osteoarthritis.

### Inclusion criteria

Subjects aged 45–85 years, living in the defined geographical areas (Västervik and Luleå municipalities in Sweden, and Trondheim and Mosjøen in Norway), who have had a diagnosis of symptomatic and radiographic verified OA grade I–III according to Kellgren and Lawrence,<sup>46 47</sup> with at least 3 months pain duration and decreased functioning. The patient is willing to participate in a 12-week intervention period with three sessions each week.

### Exclusion criteria

Physiotherapy or other conservative therapy during the previous 3 months or a history of major knee trauma such as knee fractures or ligament ruptures. Inflammatory joint disease, hip symptoms more aggravating than the knee symptoms, scheduled to have knee replacement surgery within 6 months, and comorbidities not allowing exercise such as cardiovascular, respiratory, systemic or metabolic conditions limiting exercise tolerance.

### Procedure

Before the intervention starts, regular visits will be made to each intervention site by the first author (TAT), informing and communicating to the local research team the aims and run of the study. Detailed descriptions of the different stages of the study from recruitment, treatment and follow-up assessments, after the end of the intervention period, will be instructed and discussed. Physiotherapists in charge of the objective clinical testing (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen), otherwise not involved in the treatment, will be educated theoretically and practically on how these tests should be performed. The physiotherapists delivering the exercise intervention (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen) will, in addition, have structured theoretical and practical sessions on how to apply and grade the exercise therapies. A study nurse at each intervention place is in charge of randomisation,

questionnaires, and the scheduling of patients for treatments and assessments. Each of the four intervention centres has a local administration officer.

A data security monitoring plan is conducted by the current investigator monitoring the present pragmatic trial. TAT will visit the four centres from the planning phase of the trial, during the treatment phase and during the follow-up phase in order to monitor that the protocol is followed. Adverse and serious adverse events (SAEs) are reported to the ethics committee.

Recruitment will be achieved through referrals from medical doctors (MDs) in primary and secondary health-care clinics. The local investigator at each study centre will contact MDs and send written information about the study. The first screening is performed by a MD and a second screening is performed by one of the treating physiotherapists. Both the MD and the physiotherapist guarantee the radiographic inclusion criteria.

Patients will receive oral and written information about the study, and after signing an informed consent form obtained by the local administration officer, they will be assessed for eligibility by physiotherapists at each intervention centre. Participants initially fill out questionnaires for baseline data and perform the physical performance tests. Each patient is then randomised, as described below, to either high-dose or low-dose MET.

#### Data collection and management

Data from the questionnaires will be depersonalised at each intervention centre by the local research assistant. In order to transfer data from Norway to Sweden, a data transfer agreement (DTA) between Norges Teknisk-Naturvitenskapelige Universitet/Norwegian University of Science and Technology and Karolinska Institutet, has been set up. The questionnaires from the Swedish centres are posted to Karolinska Institutet where data are registered on digital sheets. In Norway, questionnaires from Mosjøen are posted to Trondheim where all questionnaires from the two Norwegian centres are registered on sheets and delivered to Karolinska Institutet according to DTA; Tom Arild Torstensen, Björn Äng and Wilhelmus Grooten are in charge of the data synthesis and analysis.

#### Postrecruitment retention and compliance strategies

Our experiences of MET as an experimental intervention (HØ and TAT)<sup>26–35</sup> leads to the following retention and compliance strategies to be applied in this study:

- ▶ An independent study nurse at each intervention centre will always be available to answer questions when patients are filling out the questionnaires. This is important to avoid any unnecessary misunderstandings regarding the content of the questionnaire and to make sure that patients understand that all information will be depersonalised.
- ▶ During the interventions, the treating physiotherapist is present for the entire duration of the exercise in the exercise room answering questions from patients and re-grading the exercises according to changes

in patients' exercise status and knee OA symptoms. Participants are not informed about the hypothesis of the study.

- ▶ At inclusion and at the end of the 12-week intervention period the patient is informed by the local administration nurse about the 6-month and 12-month follow-ups.
- ▶ During the postintervention follow-ups, the patient will be contacted 3 weeks prior to the assessment and informed when to come to the intervention site for the planned post-treatment evaluation.

During the intervention period, the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the eight different VAS are assessed after every sixth treatment meaning after 2, 4, 6, 8, 10 and 12 weeks giving a total of six assessments. The purpose of such repeated measurements is to obtain a reasonable measurement accuracy of both functioning status and pain during the 12-week intervention period. The primary end point will be completion of the intervention after 36 treatments, which will take an average of 12 weeks. This is to obtain evaluation of effects on organised exercise therapy related with its direct implementation, while further follow-ups evaluate its retention effects. At this point primary and secondary outcomes are assessed.

#### Randomisation procedure

In this individual randomised trial, a stratified allocation by age and intervention centre is used, using a computerised programme, where the goal is to get an equal number of patients between the ages of 45 years and 64 years, and 65 years and 85 years at each of the four intervention centres. The randomisation key is concealed at each intervention place and kept locked by a research assistant not involved with the assessment or interventions.

#### Blinding procedures

The physiotherapists conducting the physical performance tests are blinded to an allocation group and the study participants are instructed by the treating physiotherapists not to reveal details of their intervention during testing. The principal investigator (BOÄ), the assistant principal investigator (TAT) and the research assistants are also blinded to groups when entering data in the data sheets, that is, they do not know which patient has received high-dose or low-dose MET. The group key will be opened after the analyses have been finalised and the results have been written in a manuscript (using interventions A and B until results have been written).

#### Interventions

All participants receive an MET intervention, where they are treated in groups of four or five in sessions lasting 20–90 min. During the sessions, the participants are supervised by an experienced physiotherapist in an outpatient clinic. All participants are treated three times a week for 12 weeks, thus giving a total of 36 treatments. Each patient in the group has an individualised exercise

**Table 1** Differences between the high-dose and low-dose medical exercise therapies (METs) regarding number of exercises, sets and repetitions. Difference in time, performing global exercises and total time duration for each treatment

	Number of exercises	Number of sets per exercise	Number of repetitions per exercise	Time performing global exercise, f.ex cycling)	Time duration of treatment
High-dose MET	9	3	30	20 min+10 min+10 min	70–90 min
Low-dose MET	5	2	10	10 min	20–30 min

programme tailored to their specific clinical symptoms and functional level. As the treatment proceeds, exercises are adapted according to changes in symptoms and functioning. The pain experience when exercising should not exceed a 3 on a 0 to 10 scale, where 0 is no pain and 10 is the worst imaginable pain.<sup>34</sup> Specially designed exercise equipment consisting of different forms of pulleys, exercise benches, dumbbells and barbells is used to grade and dose the exercises to be pain-free or close to pain-free, with the purpose of mitigating peripheral and central sensitisation while exercising.<sup>23</sup> The differences between groups regarding exercise dose is outlined in [table 1](#).

The grading of the exercises, including baseline settings, is based on the initial clinical assessment by the treating physiotherapist. From the patients' past and present histories and clinical physical assessment, information is gained about the level of pain and possible sensitisation (local versus central sensitisation), range of motion and tolerance for weight bearing within the available active range of motion (AROM) of the knee. This information is used for baseline setting of the exercises where the physiotherapist chooses a starting position (SP), a AROM, and a weight resistance (WR) believed to match the patient's ability to perform three sets of 30 repetitions (high-dose MET) and two sets of 10 repetitions (low-dose MET), pain-free or close to pain-free. Then there is a test of each exercise where the physiotherapist asks the patient to do as many repetitions as the patient can manage. When the patient reaches 10 repetitions the test is stopped and the patient has to evaluate if the WR, SP or AROM is appropriate to reach a total of 40 repetitions. Any of the above mentioned variables (WR, SP, AROM) can now be changed to reach 40 repetitions, making it possible to perform 30 repetitions in sets of three with a 30-second to 60-second pause between each. The same test procedure is used for the low-dose group where the goal is a test of 15 repetitions making it possible to do two sets of 10 repetitions. At baseline setting, there is a continuous evaluation in the exercise room where the physiotherapist and the patient are communicating working towards an optimal exercise dose for each exercise, as is usually done in clinical practice.<sup>23</sup>

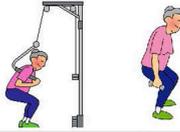
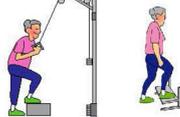
It should also be possible for the patient to perform the exercise comfortably within the preferred active range of motion, AROM. For example, if a part of AROM in the knee joint is painful, the patient starts to exercise within

the pain-free or close to pain-free AROM. As the treatment proceeds, AROM is adjusted, making the patient exercise in a larger and more functional AROM. If it is not possible to grade the exercise pain-free or close to pain-free, the patient is allowed to exercise with pain. When exercising with pain it is important that the pain experience does not cause any anxiety or fear. The pain has to be experienced as meaningful for improvement.<sup>48</sup> If the exercise therapy results in an acute increase in pain, the pain should have returned to baseline before the next treatment session commences. If pain does not go back to the prior level, exercises are reassessed, with the most comfortable exercise performed several times, preferably deloaded knee extension and stationary cycling.

The group of four to five patients also contains patients with other diagnoses, who are not participating in this study, making the delivery of the MET intervention pragmatically similar to a real life situation. To be able to monitor the exercise dose, the treating physiotherapists follow a structured progression plan of the exercises, and fill in a treatment log for each patient at each treatment, (see online supplementary appendix 1—progression plan for high-dose MET, and online supplementary appendix 2—progression plan for low-dose MET). The log contains information about the number of exercises, duration of each global exercise, number of repetitions, and sets and weight resistance applied for semiglobal and local exercises. Consent to publish the photographs in the online supplementary appendices has been obtained from the person pictured. [Figure 3](#) shows the main exercises from the two different exercise interventions compared in this planned randomised trial, high-dose MET versus low-dose MET.

To be able to reach a high number of repetitions despite ongoing pain, the principle of deloading is applied, facilitating a high number of repetitions that are nearly or entirely pain-free (see [figure 1](#)). For the high-dose MET, the deloaded knee extension is performed twice during a treatment, each time for 5 min. This exercise and the cycling in the middle of each treatment session is a form of restitution, making it easier to both perform the deloaded closed-chain exercises and endure the high-dose MET. Later, as the patient improves and can tolerate increased loading, the exercises are adapted to be more functional, using closed-chain exercises without deloading the body weight.

To further increase the exercise dose for the high-dose MET group, patients perform one home exercise—the seated deloaded knee extension with a yellow tube

EXERCISE	HIGH DOSE MET (70-90 MIN)	DOSE	LOW DOSE MET (20-30 MIN)	DOSE
1		GLOBAL 20 min		GLOBAL 10 min
2		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
3		LOCAL OPEN CHAIN 5 min		SEMI GLOBAL CLOSED CHAIN 2x10 reps
4		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
5		GLOBAL 10 min		LOCAL OPEN CHAIN 2x10 reps
6		SEMI GLOBAL CLOSED CHAIN 3x30 reps		
7		LOCAL OPEN CHAIN 5 min		
8		LOCAL OPEN CHAIN 3x30 reps		
9		GLOBAL 10 min		

**Figure 3** The two different exercise interventions compared in this randomised trial, high-dose MET (HDMET) and low-dose MET (LDMET). MET, medical exercise therapy; OA, osteoarthritis.

theraband. The exercise is similar to exercise number 3 (see figure 1). They perform this home exercise once every day, where the dose is three lots of 3 min with a 30-second to 60-second pause between each set. The treating physiotherapists make sure that the patients are compliant in doing their home exercise. Patients in the low-dose MET receive no home exercise.

#### Baseline data

The following data will be obtained by questionnaire; gender, age, height, weight, physical activity and exercise levels, living arrangement, education level, employment status, possible medication, comorbidities, smoking habits, sleeping habits, pain and function of the knee, catastrophising thoughts, fear avoidance beliefs, level

of anxiety and depression, life satisfaction and QoL, and beliefs about exercise. A schematic presentation of the outcome measures recorded at baseline and at the follow-ups is presented in table 2. Each assessment, which involves filling out questionnaires, will take approximately 1 hour. The objective testing of the knee and the testing with the PainMatcher apparatus takes approximately 30 min and will occur the following day.

#### Primary outcome measures

In accordance with international consensus regarding the core set of outcome measures for clinical trials in OA,<sup>49</sup> self-rated functioning and pain scoring (KOOS)<sup>50-53</sup> are used as primary outcome measures. KOOS consists of

**Table 2** Study measures to be collected

Baseline measures and outcomes	Description and instrument	Data source	Collection points
Patient's characteristics	Date of birth, gender, BMI (height, weight) social and living status, leisure activities, level of physical activity, smoking, medicine, sleep, comorbidities, anxiety and depression, catastrophising, life satisfaction, kinesiophobia	SAQ	t0
Primary outcome measure	Clinical outcomes		
Pain	KOOS: subscale pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Other symptoms	KOOS: subscale other symptoms	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Function	KOOS: subscale physical functioning	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Sport, recreation	KOOS: subscale sport and recreation	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Secondary outcome measures	Clinical outcomes		
	VAS (100mm scale): pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100mm scale): knee pain not loading	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100mm scale): pain at weight bearing	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100mm scale): knee pain at night	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	Physical functioning		
	20m walk test	PT	t0, t12
	Chair stand test	PT	t0, t12
	Unilateral knee bending	PT	t0, t12
	Pain threshold and tolerance		
	Pain matcher	PainMatcher apparatus	t0, t12
	Quality of life		
	(EQ-5D-5L)	SAQ	t0, t12, t26, t52
	(SF-36)	SAQ	t0, t12, t26, t52
	Life satisfaction		
	LISAT	SAQ	t0, t12, t26, t52
	Psychological outcomes		
	Anxiety and depression (HAD Scale),	SAQ	t0, t12, t26, t52
	Catastrophising (PCS)	SAQ	t0, t12, t26, t52
	Kinesiophobia (TSK)	SAQ	t0, t12, t26, t52
	Beliefs and attitude towards exercise		
	SEE Scale	SAQ	t0, t12, t26, t52
	OEE Scale	SAQ	t0, t12, t26, t52

Data source: Self-administered questionnaire (SAQ), physical testing (PT).

Collection points: t0=inclusion, t1–t12=measurement every second week during the 12-week intervention period, t1=2 weeks, t2=4 weeks, t3=6 weeks, t4=8 weeks, t5=10 weeks, t6=12 weeks (end of inclusion), t26=6 months follow-up, t52=12 months follow-up.

BMI, body mass index; EQ-5D-5L, EuroQol-5D-5L; HAD, Hospital Anxiety and Depression; KOOS, Knee Injury and Osteoarthritis Outcome Score; LISAT, Life Satisfaction Questionnaire; OEE, Outcome Expectancy for Exercise; PCS, Pain Catastrophising Scale; SEE, Self-Efficacy for Exercise; SF-36, Short Form Health Survey; TSK, Tampa Scale of Kinesiophobia; VAS, Visual Analogue Scale.

five subscales; pain, other symptoms, functioning in daily living, functioning in sport and recreation (sport/rec) and knee-related QoL. Standardised answer options are given (five Likert boxes) and each question is assigned a score from 0 to 4. A normalised score (100 indicating no symptoms and 0 indicating extreme symptoms) is

calculated for each subscale. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. We are planning to use KOOS at several time points; at baseline, and during the intervention period until the final follow-up at 52 weeks (see [table 2](#)).

## Secondary outcome measures

As a secondary outcome measure, there are eight different pain measurements using a 100mm Visual Analogue Scale (VAS),<sup>54</sup> with terminal descriptors of 'no pain' and 'worst pain' asking about how painful the knee is, (1) today and (2) on average during the last week, related to the following four different life situations; (1) how painful is your knee, (2) how painful is your knee when loading your knee (eg, walking or standing), (3) how painful is your knee when not loading your knee (eg, sitting, lying), (4) how painful is your knee at night when you are sleeping (eg, knee pain that disturbs your sleep). Data on health related QoL are collected using the EuroQol (EQ 5-D Questionnaire)<sup>55</sup> and the Short Form Health Survey (SF-36 Questionnaire).<sup>56</sup> These questionnaires will also be used to perform a health economic evaluation of the exercise interventions. Psychological factors such as anxiety and depression, catastrophising and fear-avoidance beliefs are believed to both predict outcome of an intervention<sup>57</sup> as well as influence the level of pain in patients with knee OA experience.<sup>58</sup> In this study, anxiety and depression are rated using the Hospital Anxiety and Depression Scale (HAD),<sup>59</sup> catastrophising is rated using the Pain Catastrophising Scale (PCS)<sup>60</sup> and fear avoidance beliefs<sup>61</sup> are rated using the Tampa Scale of Kinesiophobia (TSK),<sup>62</sup> (table 2). Life satisfaction is assessed using the Life Satisfaction Questionnaire by Fugl-Meyer (LISAT).<sup>63</sup> Beliefs and attitudes towards exercise are rated using the Self-Efficacy for Exercise Scale (SEE)<sup>64</sup> and the patient's expectations of performing physical activity are rated using the Outcome Expectancy for Exercise (OEE) Scale.<sup>65</sup> PainMatcher apparatus<sup>66</sup> is used to record sensory level, pain level and pain tolerance level. It works by pressing the thumb and first finger against a button on each side of the handheld PainMatcher apparatus; an electrode under each button activates an electrical current. As long as the pressure is kept against the buttons, the electrical current will slowly increase where the first sensation of the current is a measurement of sensory threshold. As the pressure is maintained, the electrical current slowly increases, and the sensation will turn into a pain sensation (pain threshold). Keeping the pressure on the buttons, the painful electrical current increases, and pain tolerance is recorded, that is, the measure of how painful an electrical current the patient can endure. Performance tests include the 20-metre walk test,<sup>67</sup> first at a self-selected pace and then at maximum pace, the 30-second maximum number of chair to standing tests<sup>68</sup> and the 30-seconds maximum number of repeated unilateral knee bends.<sup>67 69</sup> Other measurements, logged by the supervising therapist, are recordings of compliance of the exercise treatments during the 12-week intervention also including a recording of exercise dose (weights, sets, repetitions and treatment time) at each treatment occasion. Over the whole project period, from inclusion to end of the 52-week follow-up, any adverse effects are to be noted and reported.

## Statistical analysis

In the statistical analyses of both primary and secondary outcomes, the principle of intention to treat will be used, comparing high-dose MET with low-dose MET. Within-group and intergroup statistical testing will be carried out using the general linear model where an  $\alpha$  level of 0.05 will be used where appropriate. Significance of main or interaction effects will be explored using follow-up post hoc tests. Effect size Cohen's *d* will aid clinical interpretation of the magnitude of treatment effect, where effect-size values below 0.2 will be considered small, 0.5 medium and 0.8 large. The primary end point is at the end of the 12-week intervention period and potential baseline differences will be considered by adding additional baseline variables as covariates to the statistical models. Potential floor or ceiling effects will be computed and considered in our analyses. Because participants of both interventions of both intervention groups are treated together with other patients in the MET groups, the treatment credibility and outcome expectations (OEE) will be evaluated as a potential covariate or confounder for treatment effects.

Analysis of cost-effectiveness will be performed using ICER, in order to provide a single measure for weighing costs against benefits of healthcare interventions. Cost per QALY,<sup>70</sup> using data from EQ-5D and SF-36, will be added. In the predictive analyses, multivariable logistic regressions (eg, Generalised Estimating Equation (GEE)) will be used to estimate the association between potential predictors and outcomes. A purposeful selection procedure is planned resulting in a final model that contains only significant independent variables, identified confounders and interactions. All final models will be examined for goodness of fit and accuracy according to established methods.

## Sample size

The power calculation was based on proportions that can document a minimal clinically important change. The primary outcome, KOOS is a numerical scale ranging from 0 (maximal problem) to 100 (no problem). A change of 10 points is evaluated as a clinically interesting change.<sup>51</sup> The hypothesis is that 40% of the patients receiving high-dose MET and 20% of the patients receiving low-dose MET will obtain a 10-point improvement after end of treatment at the 3-month follow-up. The power calculation showed that 82 patients are needed in each arm to reach 80% between-group power. With a hypothetical dropout of the study of 20% the total sample is  $82 \times 2 \times 1.2 = 197$  patients. We plan to include 200 patients giving each exercise intervention group a total of 100 participants.

## ETHICS AND DISSEMINATION

The guidelines from the Helsinki declaration will be followed and the protocol has been approved by the Regional Ethics Review Board in Stockholm. Some relevant ethical considerations related to this study are mentioned below.

### The infliction of pain

An often overlooked ethical issue is the infliction of pain when instructing patients to exercise.<sup>19</sup> Knee OA is commonly a painful condition and it is questionable if it is ethical to push patients through the painful exercise regimens included in the approach that today is recommended for treating knee OA. A worst-case scenario for this type of treatment is pushing the patient into endurance behaviour that in itself may result in long-term pain.<sup>71</sup> However, in this study, the focus on grading the exercises pain-free or close to pain-free, to some extent, resolves this problem.

### The problem of large exercise dosage

Asking patients to exercise for 70–90 min three times a week for 12 weeks may be ethically questionable. However, such doses of exercise therapy have been shown to be effective in patients with depression<sup>72</sup> and there is an argument today that both exercise dose and exercise intensity should be increased for patients suffering from heart disease and a metabolic syndrome, respectively.<sup>73</sup> The high compliance with a relatively extensive exercise programme is possible because patients with chronic (or progressed) conditions commonly prioritise rehabilitation to maintain (or improve) good functioning. Thus, there is a need to investigate if a similar high dose of exercise therapy is effective for patients with knee OA. It is also of high relevance to study whether a less time-consuming exercise programme, such as the low-dose MET in the present study, results in similar effects including effects on costs.

## DISCUSSION

We believe one important strength of this study is the use of self-paced exercises, grading the exercises pain-free or close to pain-free.<sup>36</sup> Research has shown that when patients are asked to self-select their exercise intensity, they choose an intensity that results in a positive affective response making them more motivated to do the exercise. This seems to be the case for both, populations without pain<sup>74</sup> and patients suffering from a painful condition.<sup>75</sup> The use of a self-paced approach, exercising pain-free or close to pain-free may—we believe—decrease the probability of patients dropping out of the study due to adverse effects such as uncomfortable painful experiences,<sup>36 75</sup> which minimises possible nocebo effects,<sup>76</sup> and breaks the vicious circle of knee pain.<sup>23</sup>

To decrease negative affective experiences from exercising, MET applies the principle of deloading, where the application of different types of exercise equipment deloads some of the body weight or the weight of the lower extremity. This is also the case for aquatic exercise therapy where the buoyancy of the water decreases compressive forces on the knee joint. However, aquatic exercises do not seem to be superior to land-based exercises,<sup>77</sup> making a call for further research into dose-response effects from exercise therapy.

In an extensive review by Pedersen and Saltin,<sup>78</sup> it was concluded that there is evidence for prescribing exercise as a therapy for 26 different chronic diseases. In addition,

there is increasing evidence that a higher dose of exercise is more effective than a lower dose in patients with long-term subacromial pain<sup>34</sup> and long-term anterior knee pain,<sup>27</sup> patients with depression<sup>72</sup> and patients with a metabolic syndrome.<sup>73</sup> A high dose of exercise has a greater effect on heart function<sup>79</sup> and a greater positive impact on mood states and QoL<sup>80</sup> in patients with heart failure.

In terms of knee OA, however, the evidence level of exercise dose is poor.<sup>12 13 22 78 81 82</sup> In a recent systematic review<sup>13</sup> only five studies that compared high-intensity versus low-intensity physical activity were included. Of these five studies, there is only one study<sup>17</sup> that is in any way similar to this planned study. The study<sup>17</sup> compared high-intensity versus low-intensity cycle ergometry in older adults with knee OA. Both groups cycled for 25 min three times a week for 10 weeks. The high-dose high-intensity group cycled with an intensity of 70% of HRR and the low-dose low-intensity group with an intensity of 40% of HRR. After the end of the intervention period both groups had improved significantly on all outcome measures but there were no differences between groups. Juhl *et al*<sup>82</sup> argue that an optimal exercise programme for knee OA should focus on improving quadriceps strength and aerobic capacity, as well as improving performance in the lower extremities. Exercise programmes should be supervised and carried out three times a week. They also argue that there is a great need to further investigate the effects of differing exercise doses and that the interventions in such studies are described in detail with regard to intensity, length of programme, total number of supervised sessions, duration of individual supervised sessions and number of sessions per week.

To our knowledge, this study is the first to investigate, in a controlled manner, if an exercise dose lasting 70–90 min is superior in terms of improvements in functioning and pain to a lower dose of exercise therapy lasting 20–30 min in patients with knee OA.

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## REFERENCES

- Nguyen US, Zhang Y, Zhu Y, *et al.* Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011;155:725–32.
- Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol* 2014;28:5–15.
- Cross M, Smith E, Hoy D, *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323–30.
- Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005;365:965–73.
- March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. *Baillieres Clin Rheumatol* 1997;11:817–34.
- Pereira D, Peleteiro B, Araujo J, *et al.* The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage* 2011;19:1270–85.
- Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). *Exp Brain Res* 2010;205:1–12.
- Arendt-Nielsen L. Joint pain: more to it than just structural damage? *Pain* 2017;158(Suppl 1):S66–73.
- Fingleton C, Smart K, Moloney N, *et al.* Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:1043–56.
- Tornbjerg SM, Nissen N, Englund M, *et al.* Structural pathology is not related to patient-reported pain and function in patients undergoing meniscal surgery. *Br J Sports Med* 2017;51:525–30.
- Thorstensson CA, Andersson ML, Jönsson H, *et al.* Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Ann Rheum Dis* 2009;68:1890–3.
- Fransen M, McConnell S, Harmer AR, *et al.* Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med* 2015;49:1554–7.
- Regnaux JP, Lefevre-Colau MM, Trinquart L, *et al.* High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database Syst Rev* 2015:CD010203.
- Ageberg E, Roos EM. Neuromuscular exercise as treatment of degenerative knee disease. *Exerc Sport Sci Rev* 2015;43:14–22.
- Knoop J, Dekker J, van der Leeden M, *et al.* Knee joint stabilization therapy in patients with osteoarthritis of the knee: a randomized, controlled trial. *Osteoarthritis Cartilage* 2013;21:1025–34.
- Latham N, Liu CJ. Strength training in older adults: the benefits for osteoarthritis. *Clin Geriatr Med* 2010;26:445–59.
- Mangione KK, McCully K, Gloviak A, *et al.* The effects of high-intensity and low-intensity cycle ergometry in older adults with knee osteoarthritis. *J Gerontol A Biol Sci Med Sci* 1999;54:M184–90.
- Henriksen M, Rosager S, Aaboe J, *et al.* Experimental knee pain reduces muscle strength. *J Pain* 2011;12:460–7.
- Liu CJ, Latham N. Adverse events reported in progressive resistance strength training trials in older adults: 2 sides of a coin. *Arch Phys Med Rehabil* 2010;91:1471–3.
- Henriksen M, Klokner L, Graven-Nielsen T, *et al.* Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res* 2014;66:1836–43.
- Campbell CM, Buenaver LF, Finan P, *et al.* Sleep, Pain Catastrophizing, and Central Sensitization in Knee Osteoarthritis Patients With and Without Insomnia. *Arthritis Care Res* 2015;67:1387–96.
- Hurley MV, Mitchell HL, Walsh N. In osteoarthritis, the psychosocial benefits of exercise are as important as physiological improvements. *Exerc Sport Sci Rev* 2003;31:138–43.
- Lorås H, Østerås B, Torstensen TA, *et al.* Medical Exercise Therapy for Treating Musculoskeletal Pain: A Narrative Review of Results from Randomized Controlled Trials with a Theoretical Perspective. *Physiother Res Int* 2015;20:182–90.
- Crombez G, Vlaeyen JW, Heuts PH, *et al.* Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain* 1999;80(1-2):329–39.
- Bartholdy C, Juhl C, Christensen R, *et al.* The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and meta-regression analysis of randomized trials. *Semin Arthritis Rheum* 2017;47:9–21.
- Torstensen TA, Meen HD, Stiris M. The effect of medical exercise therapy on a patient with chronic supraspinatus tendinitis. Diagnostic ultrasound--tissue regeneration: a case study. *J Orthop Sports Phys Ther* 1994;20:319–27.
- Østerås B, Østerås H, Torstensen TA, *et al.* Long-term effects of medical exercise therapy in patients with patellofemoral pain syndrome: results from a single-blinded randomized controlled trial with 12 months follow-up. *Physiotherapy* 2013;99:311–6.
- Østerås B, Østerås H, Torstensen TA, *et al.* Dose-response effects of medical exercise therapy in patients with patellofemoral pain syndrome: a randomised controlled clinical trial. *Physiotherapy* 2013;99:126–31.
- Østerås H. A 12-week medical exercise therapy program leads to significant improvement in knee function after degenerative meniscectomy: a randomized controlled trial with one year follow-up. *J Bodyw Mov Ther* 2014;18:374–82.
- Osteras B, Torstensen TA. Medical Exercise Therapy is Effective After Arthroscopic Surgery of Degenerative Meniscus of the Knee: A Randomized Controlled Trial. *J Clin Med Res* 2012;4:378–84.
- Østerås H, Østerås B, Torstensen TA. Medical exercise therapy, and not arthroscopic surgery, resulted in decreased depression and anxiety in patients with degenerative meniscus injury. *J Bodyw Mov Ther* 2012;16:456–63.
- Østerås H, Østerås B, Torstensen TA. Is postoperative exercise therapy necessary in patients with degenerative meniscus? A randomized controlled trial with one year follow-up. *Knee Surg Sports Traumatol Arthrosc* 2014;22:200–6.
- Østerås H, Torstensen TA. The dose-response effect of medical exercise therapy on impairment in patients with unilateral longstanding subacromial pain. *Open Orthop J* 2010;4:1–6.
- Østerås H, Torstensen TA, Østerås B. High-dosage medical exercise therapy in patients with long-term subacromial shoulder pain: a randomized controlled trial. *Physiother Res Int* 2010;15:232–42.
- Østerås H, Arild Torstensen T, Arntzen G, *et al.* A comparison of work absence periods and the associated costs for two different modes of exercise therapies for patients with longstanding subacromial pain. *J Med Econ* 2008;11:371–81.
- Williams DM. Exercise, affect, and adherence: an integrated model and a case for self-paced exercise. *J Sport Exerc Psychol* 2008;30:471–96.
- Torstensen TA, Ljunggren AE, Meen HD, *et al.* Efficiency and costs of medical exercise therapy, conventional physiotherapy, and self-exercise in patients with chronic low back pain. A pragmatic,

- randomized, single-blinded, controlled trial with 1-year follow-up. *Spine* 1998;23:2616–24.
38. McAlindon TE, Driban JB, Henrotin Y, *et al.* OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage* 2015;23:747–60.
  39. Deyle GD, Gill NW, Allison SC, *et al.* Knee OA: which patients are unlikely to benefit from manual PT and exercise? *J Fam Pract* 2012;61:E1–8.
  40. Laisné F, Lecomte C, Corbière M. Biopsychosocial predictors of prognosis in musculoskeletal disorders: a systematic review of the literature (corrected and republished) \*. *Disabil Rehabil* 2012;34:1912–41.
  41. Fuentes C JP, Armijo-Olivo S, Magee DJ, *et al.* Effects of exercise therapy on endogenous pain-relieving peptides in musculoskeletal pain: a systematic review. *Clin J Pain* 2011;27:365–74.
  42. Koitlyn KF. Exercise-induced hypoalgesia and intensity of exercise. *Sports Med* 2002;32:477–87.
  43. Naugle KM, Naugle KE, Fillingim RB, *et al.* Intensity thresholds for aerobic exercise-induced hypoalgesia. *Med Sci Sports Exerc* 2014;46:817–25.
  44. Boecker H, Sprenger T, Spilker ME, *et al.* The runner's high: opioidergic mechanisms in the human brain. *Cereb Cortex* 2008;18:2523–31.
  45. Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2011;9:672–7.
  46. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
  47. Schiphof D, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Ann Rheum Dis* 2008;67:1034–6.
  48. Benedetti F, Thoen W, Blanchard C, *et al.* Pain as a reward: changing the meaning of pain from negative to positive co-activates opioid and cannabinoid systems. *Pain* 2013;154:361–7.
  49. Bellamy N, Kirwan J, Boers M, *et al.* Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;24:799–802.
  50. Roos EM. Effectiveness and practice variation of rehabilitation after joint replacement. *Curr Opin Rheumatol* 2003;15:160–2.
  51. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003;1:64.
  52. Roos EM, Roos HP, Ekdahl C, *et al.* Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scand J Med Sci Sports* 1998;8:439–48.
  53. Roos EM, Roos HP, Lohmander LS, *et al.* Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.
  54. Lundeberg T, Lund I, Dahlin L, *et al.* Reliability and responsiveness of three different pain assessments. *J Rehabil Med* 2001;33:279–83.
  55. Fransen M, Edmonds J. Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. *Rheumatology* 1999;38:807–13.
  56. Sullivan M, Karlsson J, Ware JE. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Soc Sci Med* 1995;41:1349–58.
  57. Orenius T, Koskela T, Koho P, *et al.* Anxiety and depression are independent predictors of quality of life of patients with chronic musculoskeletal pain. *J Health Psychol* 2013;18:167–75.
  58. Urquhart DM, Phymaung PP, Dubowitz J, *et al.* Are cognitive and behavioural factors associated with knee pain? A systematic review. *Semin Arthritis Rheum* 2015;44:445–55.
  59. Bjelland I, Dahl AA, Haug TT, *et al.* The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:69–77.
  60. Osman A, Barrios FX, Kopper BA, *et al.* Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med* 1997;20:589–605.
  61. Holla JF, Sanchez-Ramirez DC, van der Leeden M, *et al.* The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. *J Behav Med* 2014;37:1226–41.
  62. Lundberg M, Grimby-Ekman A, Verbunt J, *et al.* Pain-related fear: a critical review of the related measures. *Pain Res Treat* 2011;2011:1–26.
  63. Fugl-Meyer AR, Eklund M, Fugl-Meyer KS. Vocational rehabilitation in northern Sweden. III. Aspects of life satisfaction. *Scand J Rehabil Med* 1991;23:83–7.
  64. Resnick B, Jenkins LS. Testing the reliability and validity of the Self-Efficacy for Exercise scale. *Nurs Res* 2000;49:154–9.
  65. Resnick B, Zimmerman SI, Orwig D, *et al.* Outcome expectations for exercise scale: utility and psychometrics. *J Gerontol B Psychol Sci Soc Sci* 2000;55:S352–6.
  66. Kowalski J, Lundeberg T. A new highly reliable instrument for the assessment of pre- and postoperative gynecological pain. *Anesth Analg* 2002;95:151–7.
  67. Villadsen A, Roos EM, Overgaard S, *et al.* Agreement and reliability of functional performance and muscle power in patients with advanced osteoarthritis of the hip or knee. *Am J Phys Med Rehabil* 2012;91:401–10.
  68. Dobson F, Hinman RS, Hall M, *et al.* Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis Cartilage* 2012;20:1548–62.
  69. Bremander AB, Dahl LL, Roos EM. Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis. *Scand J Med Sci Sports* 2007;17:120–7.
  70. Prieto L, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes* 2003;1:80.
  71. Hasenbring MI, Chehadi O, Titz C, *et al.* Fear and anxiety in the transition from acute to chronic pain: there is evidence for endurance besides avoidance. *Pain Manag* 2014;4:363–74.
  72. Dunn AL, Trivedi MH, Kampert JB, *et al.* Exercise treatment for depression: efficacy and dose response. *Am J Prev Med* 2005;28:1–8.
  73. Slentz CA, Houmard JA, Kraus WE. Exercise, abdominal obesity, skeletal muscle, and metabolic risk: evidence for a dose response. *Obesity* 2009;17(Suppl 3):S27–33.
  74. Ekkkekakis P. People have feelings! Exercise psychology in paradigmatic transition. *Curr Opin Psychol* 2017;16:84–8.
  75. Dipnarine K, Barak S, Martinez CA, *et al.* Pain-free treadmill exercise for patients with intermittent claudication: Are there gender differences? *Vascular* 2016;24:304–14.
  76. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol* 2007;20:435–9.
  77. Bartels EM, Juhl CB, Christensen R, *et al.* Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2016;3:CD005523.
  78. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports* 2015;25(Suppl 3):1–72.
  79. Wisloff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev* 2009;37:139–46.
  80. Evangelista LS, Cacciata M, Stromberg A, *et al.* Dose-Response Relationship Between Exercise Intensity, Mood States, and Quality of Life in Patients With Heart Failure. *J Cardiovasc Nurs* 2017;32:530–7.
  81. Hurley MV. Muscle dysfunction and effective rehabilitation of knee osteoarthritis: what we know and what we need to find out. *Arthritis Rheum* 2003;49:444–52.
  82. Juhl C, Christensen R, Roos EM, *et al.* 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* 2014;66:622–36.