Influence of the physical environment on treatment effect in exercise therapy for knee or hip pain

Research Unit for Musculoskeletal Function and Physiotherapy

Department of Sport Science and Clinical Biomechanics

Faculty of Health Sciences

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Ph.D. Thesis

Odense 2016

CONTENT

Preface

This thesis was completed at the Department of Sport Science and Clinical Biomechanics, Faculty of Health Science at The University of Southern Denmark, Odense. Main supervisor was Professor Ewa M. Roos (University of Southern Denmark). Associate Professor Jonas Bloch Thorlund (University of Southern Denmark) and Research Fellow Andrew J. Moore (University of Bristol) acted as co-supervisors.

The thesis includes a randomised controlled clinical trial of 103 participants with knee or hip pain exercising in either a contextually enhanced environment or a standard environment and a nested qualitative study. The intervention and all testing took place at the Research Unit for Musculoskeletal Function and Physiotherapy at the Department of Sports and Clinical Biomechanics, University of Southern Denmark. Recruitment into the trial was accomplished through general practitioners and ads in local news media and social media.

The trial was supported by The Swedish Research Council, Good Life with Osteoarthritis in Denmark, the Faculty of Health Science at University of Southern Denmark, and the Danish Rheumatism Association.

List of papers

The thesis is comprised of the following three articles. The papers will be referred to with their roman numbers throughout the thesis. Papers I and II have been published. Paper III has been submitted for publication.

I) Sandal LF, Thorlund JB, Ulrich RS, Dieppe PA, Roos EM, 2015. Exploring the effect of space and place on response to exercise therapy for knee or hip pain—a protocol for a double-blind randomised controlled trial: The CONEX trial. BMJ Open 5 e007701.

II) Sandal LF, Roos EM, Bøgesvang SJ, Thorlund JB, 2015. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. Osteoarthritis & Cartilage xxx (2015) 1-4 [article in press].

III) Sandal LF, Thorlund JB, Moore AJ, Ulrich RU, Dieppe PA, Roos, EM, 2016: Influence of the physical environment on the effect of exercise therapy for knee or hip pain—a mixed-method randomized controlled trial. [submitted]

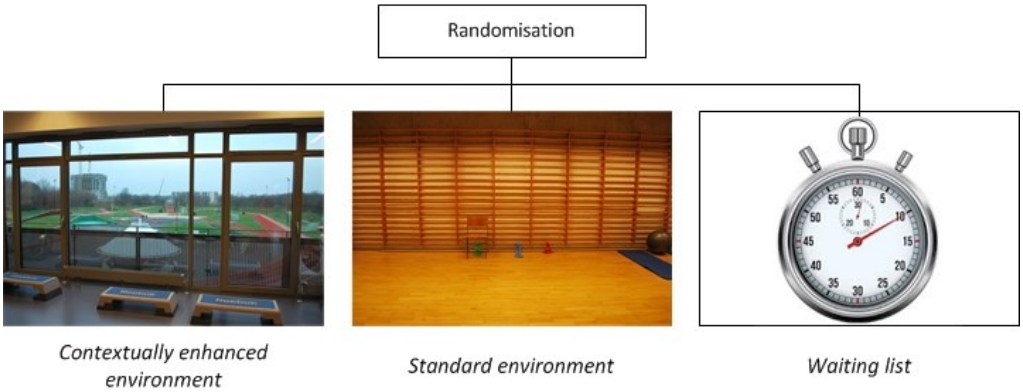
Thesis at a glance

Paper I & III: Does the physical environment influence the effect of exercise therapy as treatment for musculoskeletal pain?

Aim: To investigate the influence of the physical environment on treatment response to exercise therapy

Participants: 42 exercising in a contextually enhanced environment
40 exercising in a standard environment
21 on a passive waiting list

Methods: Randomised controlled double-blind trial comparing exercise therapy performed in a contextually enhanced environment with a standard environment. Primary outcome: Participants Global Perceived Effect. Nested qualitative interviews with participants and therapists from the two exercise environments



Conclusion: The trial results indicate that the physical environment does influence treatment effect from exercise therapy. The qualitative study suggested that matching the physical environment to the attitudes and preferences of the intended users may enhance patient-reported treatment effects from exercise therapy

Paper II: How does joint pain and acute exercise-induced pain flares change during an 8 week exercise therapy programme?

Aim: To investigate the trajectory of joint pain and acute exercise-induced pain flare during 8 weeks of supervised neuromuscular exercise therapy

Participants: 82 exercising participants
(Exercise groups from paper III combined)

Methods: Participants rating joint pain on an 11-point Numerical Rating Scale at baseline and 8-weeks-follow-up as well as before and after every attended exercise session

Conclusion: A clear decrease in size of acute exercise-induced pain flares and joint pain with increasing number of exercise sessions was seen during an eight-week neuromuscular exercise therapy programme

Description of contributions

Paper I

Study design:	Louise F. Sandal Jonas B. Thorlund Roger S. Ulrich Paul Dieppe Ewa M. Roos
Data collection	
Data analysis	
Manuscript writing	Louise F. Sandal
Manuscript revision	Louise F. Sandal Jonas B. Thorlund Roger S. Ulrich Paul Dieppe Ewa M. Roos
Journal contract	Louise F. Sandal

Paper II

Study design:	Louise F. Sandal Jonas B. Thorlund
Data collection	Louise F. Sandal Signe J. Bøgesvang
Data analysis	Louise F. Sandal
Manuscript writing	Louise F. Sandal
Manuscript revision	Louise F. Sandal Ewa M. Roos Signe J. Bøgesvang Jonas B. Thorlund
Journal contact	Louise F. Sandal

Paper III

Study design:	Louise F. Sandal Jonas B. Thorlund Andrew J. Moore Roger S. Ulrich Paul Dieppe Ewa M. Roos
Data collection	Louise F. Sandal
Data analysis	Carsten Juhl Louise F. Sandal Andrew J. Moore Paul Dieppe
Manuscript writing	Louise F. Sandal
Manuscript revision	Louise F. Sandal Jonas B. Thorlund Andrew J. Moore Roger S. Ulrich Paul Dieppe Ewa M. Roos
Journal contact	Louise F. Sandal

Abbreviations

ASES:	Arthritis Self-Efficacy Scale
BMI:	Body Mass Index
CI:	Confidence Interval
C50:	Clarity index for initial 50 msec
EX:	Exercise in a standard environment
EX+ROOM:	Exercise in a contextually enhanced environment
FG:	Focus Group interview
GPE:	Participant's Global Perceived Effect
HOOS:	the Hip disability and Osteoarthritis Outcome Score
KOOS:	the Knee injury and Osteoarthritis Outcome Score
NEMEX:	Neuromuscular exercise therapy programme
NRS:	Numerical Rating Scale
OA:	Osteoarthritis
PPM:	Parts Per Million
RCT:	Randomised Controlled Trial
SD:	Standard Deviation
SF-36:	Short-Form (36 item) Health Survey
STI:	Speech Transmission Index
T20:	Time for 20dB decay
VAS:	Visual Analogue Scale
WL:	Waiting List

Definitions

Participants:	Participants included in the randomised controlled trial.
Primary investigator:	The author of the thesis.
Research secretary:	An employee at the research unit for musculoskeletal function and physiotherapy, who handled the randomisation in relation to the trial, but not otherwise involved in the trial design or conduct.
Research team:	Supervisors or co-authors of the paper in question.
Therapists:	Physiotherapists certified in supervising the neuromuscular exercise therapy.

1. INTRODUCTION

1.1 Context effects

Context effects are defined as the effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context in which the treatment is given (Kleijnen et al. 1994, Di Blasi et al. 2001, Kaptchuk 2002, Koshi et al. 2007, Miller et al. 2008). The concept of context effects is multifactorial and the term context should be interpreted broadly as a variety of factors including physical, mental, and social factors that may contribute to the context of any given treatment (Miller et al. 2008).

An example of context effects is a study by Kaptchuk et al., who investigated the quality of the patient-practitioner relationship in patients with irritable bowel syndrome treated with acupuncture. The study found that patients treated by a warm, emphatic practitioner had better treatment response than patients treated by a practitioner who limited dialogue and interaction with the patients despite both groups being given similar acupuncture (Kaptchuk et al. 2008).

1.1.1 Context effects and placebo effect

Context effects as a term originally developed from the discussion about placebo effect. Placebo has been known and used for centuries. The use of placebo as an inert comparator to new active treatment in randomised controlled trials (RCT) is essential to ensure efficiency of treatments, as Beecher stated in his paper "The Powerful Placebo" (Beecher 1955). With the use of placebo there followed discussion about placebo effect and whether placebo has therapeutic effects, despite being an inert treatment.

During this discussion, several authors objected to the term placebo effect, as they argue that the definition is self-contradicting and inadequate (Grunbaum 1981, Margo 1999, Barrett et al. 2006, Miller et al. 2008, Breidert et al. 2009). Placebos are classically defined as inert treatments (Margo 1999, Koshi et al. 2007). However, if placebos are inert, they cannot have an effect, and, if they have an effect, they cannot be inert (Margo 1999, Barrett et al. 2006, Koshi et al. 2007, Miller et al. 2008). Consequently, several other terms have been suggested to better describe the phenomenon of therapeutic effect, not directly related to the specific treatment. These terms include incidental effects (Paterson et al. 2005), non-specific effects (Kaptchuk et al. 2008, Miller et al. 2008), meaning response (Moerman et al. 2002), and context effects (Di Blasi et al. 2001), the latter being applied in this thesis.

Although context effects have parallels to placebo effect, a clear distinction between the two concepts should be made. Context effects address the additive or enhanced effect of an existing

treatment by optimising the treatment context (Di Blasi et al. 2001, Kaptchuk 2002, Koshi et al. 2007, Miller et al. 2008, Sütterlin et al. 2015), whereas the placebo effect is associated with giving inert treatment and entails a form of deliberate deception (Kaptchuk 1998). In recent years, the discussion about placebo and context effects has turned from debating *whether* such effects exist to discussing the distinction between the concepts and their potential to enhance treatment effects (Miller et al. 2008, Bystad et al. 2015, Sütterlin et al. 2015). As a result, more research has been undertaken to investigate the underlying factors and mechanisms contributing to context effects.

1.1.2 Context factors

Several factors have been hypothesised to contribute to context effects. In a review, Di Blasi et al. focussed on emotional and cognitive care in the patient-practitioner relationship, but identified several categories of contextual factors that contribute to context effects (Di Blasi et al. 2001). In addition to the patient-practitioner relationship, these factors include: patient's characteristics, practitioner's characteristics, treatment characteristics, and the health-care setting (the physical environment) (Figure 1).

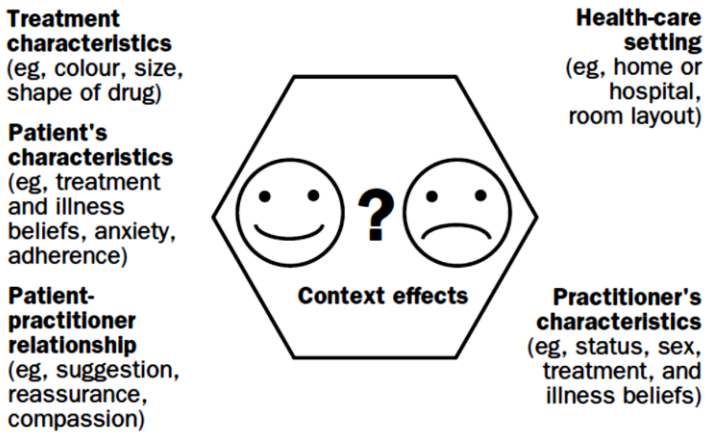


Figure 1: Categories of factors that may contribute to context effects. Figure from Di Blasi et al., 2001. Reprinted with permission.

The *patient and practitioner relationship* as context factor has been thoroughly studied (Stewart 1995, Di Blasi et al. 2001, Kelley et al. 2014). Initially, the practitioners' communication style in general practice was investigated as a component of this relationship (Thomas 1987, Thomas 1994, Essers et al. 2013). More recently, studies have focused on other health-care professionals and other treatment settings (Lang et al. 2005, Kaptchuk et al. 2008, Bensing et al. 2010, Reinders et al. 2011).

As an example, Suarez-Almazor et al. found that acupuncturists expressing high expectations towards treatment effect resulted in greater pain relief for patients with knee osteoarthritis (OA) compared to acupuncturists expressing neutral expectations (Suarez-Almazor et al. 2010).

Practitioner's characteristics have been studied less as context factor. As an example, a study by White et al. investigated consultation style during acupuncture (White et al. 2012). The study did not find an effect of communication style, but did find an effect of practitioner's characteristics, as one specific acupuncturist had better treatment outcomes than the two other acupuncturists in the trial. Interviews showed that participants attributed more authority to that one particular acupuncturist, supporting practitioner's characteristics as context factor (White et al. 2012).

For *patient characteristics,* the patient's preferences or expectations towards treatment have been investigated. Bower et al. reported results of a systematic review on patient preference and found that patients treated in accordance with their preference report better treatment response (Bower et al. 2005). Other patient's characteristics such as culture and previous experience with the health-care system may also influence the treatment context (Di Blasi et al. 2001, Watson et al. 2012, Abhishek et al. 2013).

Treatment characteristics have especially been investigated in studies of placebo effect. The brand, size, and colour of pills are factors known to influence treatment response in medical studies (Doherty et al. 2009, Abhishek et al. 2013). Also, a dose-response-like relationship has been found in method of delivery, indicating that the more invasive the treatment is (oral consumption < injection < surgery), the larger the placebo response will be (Di Blasi et al. 2001, Doherty et al. 2009, Abhishek et al. 2013, Bannuru et al. 2015).

1.1.3 Physical environment as context factor

The *physical environment* is similarly hypothesised to act as a context factor (Di Blasi et al. 2001, Doherty et al. 2009, Sütterlin et al. 2015). Previous research investigating context factors originates mostly from studies of placebo effect and studies in general practice, whereas the rationale for the physical environment as context factor builds on previous research investigating the influence of the physical environment on health-outcomes in hospital settings.

In 1984, Ulrich presented evidence that elements of the physical environment affect health outcomes (Ulrich 1984). This observational study showed that patients recovering from bowel surgery in a room with a view to nature had shorter admission time, received less pain-relieving medication, and had fewer negative remarks in nurses' journals compared to patients recovering in a room with a view to an urban environment (Figure 2) (Ulrich 1984).

Figure 2: Schematic of views during recovering from surgery in the Ulrich study, 1984. Figure reprinted with permission from Doherty et al, 2009.

Since the Ulrich study, several other studies have investigated the physical environment and its influence on health outcomes in hospital settings. Two comprehensive reviews have summarised factors known to affect treatment outcomes or perceived well-being for patients and staff in hospital settings (Table 1) (Ulrich et al. 2008, Frandsen et al. 2009). Some factors are reported to have negative influence, for example, noise levels and insufficient lighting level have negative impact on the number of medical errors and may increase pain and stress levels in patients and staff (Ulrich et al. 2008). On the other hand, studies have reported that factors such as view to nature (Ulrich 1984), higher light-intensity, and exposure to daylight (Walch et al. 2005, Malenbaum et al. 2008) and targeted sounds such as music or nature sounds (Cooke et al. 2005, Goodall et al. 2005) affect health and treatment outcomes positively.

Table 1: Factors within the physical environment in hospital settings influencing health outcome		
Factor	Health outcome	Example
Light		
Sunlight	Pain relief ↑ Sleep quality ↑ Admission length ↓ Depression ↓ Stress ↓	In a prospective study 89 patients undergoing spine surgery were "housed" in either a dim or bright room post-surgery. Bright rooms had 46% more light intensity, here patients experienced less stress, less pain and required less analgesic medication (Walch et al. 2005).
High light intensity	Pain relief ↑ Depression ↓	
Light mimicking circadian rhythm	Sleep quality ↑	
View		
Artwork	Stress ↓	In an observational study, patients recovering from surgery in a room with view to nature compared to urban views had shorter post-operative stay and required less analgesic medication (Ulrich 1984).
Nature scenes	Stress ↓ Pain relief ↑ Patient satisfaction ↑ Admission length ↓	
Noise/sound		
Noise	Stress ↑ Sleep quality ↓ Stress /job satisfaction in staff ↓	In a prospective observational study performed before, during, and after reconstruction of a hospital ward, staff perceived elevated noise level and felt it disrupted in their work (Trickey et al. 2012).
Targeted sounds (Music, nature sounds)	Pain relief ↑	
Design		
Single bed rooms	Stress ↓ Sleep quality ↑ Patient satisfaction ↑ Social support ↑ Communication ↑	A qualitative study investigated in-patients' experience of sleep during the night. Patients did not consider their amount of sleep sufficient and felt disturbed by other patients or staff, or by light intensity not dimmed for a sufficient amount of time. Single-bed rooms were suggested as a potential method of increasing sleep satisfaction (Southwell et al. 1995).
Private sitting areas	Patient satisfaction ↑ Social support ↑ Communication ↑	
Access to outdoor environments	Stress ↓ Patient satisfaction ↓ Pain relief ↑	
Table 1: ↑ indicate an increase, ↓ indicate a decrease		

Although, a vast number of studies have investigated the influence of the physical environment on health outcomes in hospital settings, research investigating other health-care settings has been sparse, including exercise therapy settings. In an initial literature search, only one previous study was identified investigating the relation between the physical environment and physical therapy (Davis 2011). However, this was an observational study using surveys and interviews to gain knowledge about design of a hospital roof-top garden rather than investigating factors within the built environment (Davis 2011). Additionally, the therapy described was occupational therapy, not regular exercise as investigated in this study. Other studies have investigated how accessibility to outdoor spaces and exercise facilities impact general activity level in children and adolescents, rather than specific factors within the built environment (Christiansen et al. 2013, Klinker et al. 2014).

Exploring the influence of the physical environment on treatment effect and health outcomes in an exercise therapy setting is of interest as exercise therapy and physical activity are potent and recommended treatments for lifestyle disease such as musculoskeletal disorders (Berra et al. 2015). The global prevalence of musculoskeletal disorders is increasing and a potential enhancement of effect from exercise therapy will be beneficial to a large number of people.

1.2 Musculoskeletal disorders and joint pain

In the World Health Organizations' Global Burden of Disease study from 2010, musculoskeletal disorders are listed as one of the major contributors globally to years lived with disability along with mental and behavioural disorders, diabetes, and endocrine diseases (Vos et al. 2012). When combined, musculoskeletal disorders were responsible for 21.3% of years lived with disability (Vos et al. 2012). The study showed that the prevalence of musculoskeletal disorders is increasing. OA was ranked 15th among diseases causing disability in 1990, whereas in 2010 it was ranked 11th, indicating a 64% increase over 20 years (Vos et al. 2012).

In Denmark, musculoskeletal disorders are the most common of the chronic diseases (Holmberg et al. 2015). It is estimated that over half of the population frequently experience pain from muscles, joints, or bones (Roos et al. 2013). Persons with musculoskeletal disorders present with symptoms such as pain, loss of physical function, and reduced quality of life (Holmberg et al. 2015). In the older population (65-74 years), 15% of males and 23% of females report pain or discomfort from hands, arms, legs, knees, hips, or joints within the past two weeks (Christensen et al. 2014).

1.2.1 Exercise as treatment for muskuloskeletal pain

Exercise therapy is a recommended first-line treatment in clinical guidelines for knee and hip OA (Hochberg et al. 2012, Sundhedsstyrelsen 2012, McAlindon et al. 2014). Patients with lower-limb OA may experience increased joint pain during physical activity or exercise and may therefore feel hesitant to start exercise therapy (Heuts et al. 2004). Hypothetically, patients may be more willing to accept transient increases in joint pain if they are informed about the expected size and duration of increased pain before starting exercise therapy. Therefore, knowledge about the expected pain relief and trajectory of pain during exercise therapy would be valuable information for clinicians and patients.

There are no specific recommendations regarding which type of exercise therapy (aerobic, strength training, neuromuscular etc.) should be preferred for patients with musculoskeletal pain, such as OA. Exercise therapy programmes that are supervised and have specific aims have been reported to relieve pain more efficiently than programmes built on generic exercise or without specific aims (Juhl et al. 2014). Despite a growing number of studies demonstrating moderate effect for relieving pain and improvement in function with exercise therapy in knee or hip OA patients, large variation in effect size is observed across studies (Fransen et al. 2014, Fransen et al. 2015). This variation may be caused by differences in exercise therapy programmes and populations. However, such variation may also relate to the fact that the exercise therapy has been performed in different physical environments influencing patients differently (Di Blasi et al. 2001).

2 AIM OF THESIS

Overall aim

- To investigate the role of the physical environment as a contributor to context effects in the treatment response from exercise therapy as treatment for musculoskeletal pain.

Specific aims

- To investigate the influence of the physical environment on treatment response to exercise therapy (Paper I + III)
- To investigate the trajectory of joint pain and acute exercise-induced pain flare during 8 weeks of supervised neuromuscular exercise therapy (Paper II)

3 METHODS (Paper I+III)

This thesis builds on previous research in three areas: exercise therapy as treatment for musculoskeletal pain, the physical environment in health-care settings, and context effects (Figure 3). Consequently, several different outcomes and methods commonly used in these different research areas were included in the study. In addition, the RCT was designed as a mixed-method study and therefore both qualitative and quantitative data were collected, analysed, and used in the interpretation of the study results.

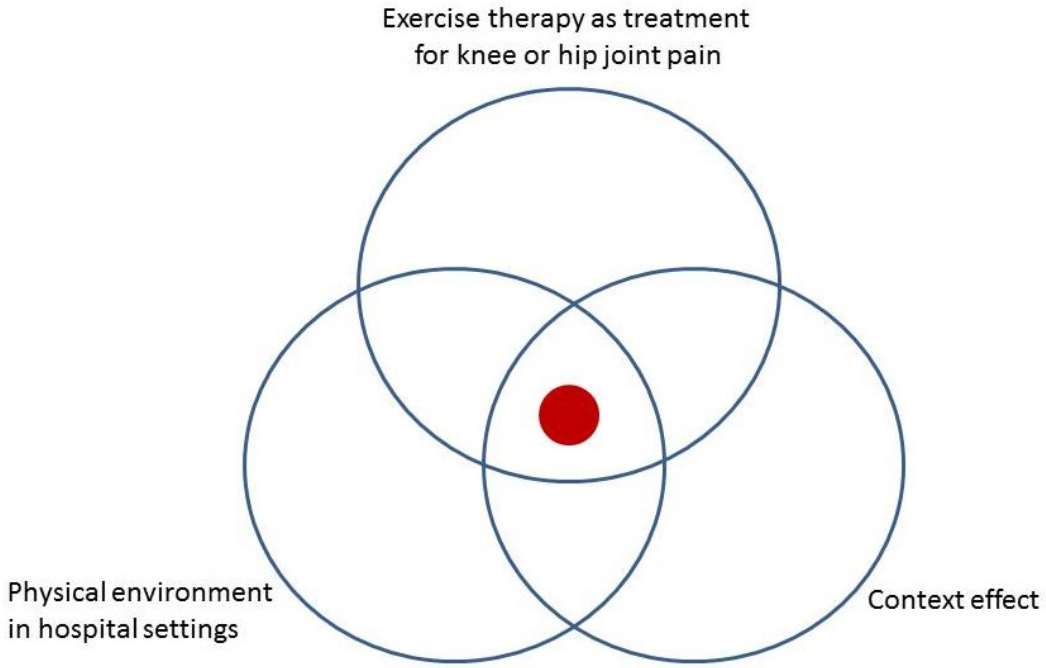


Figure 3: Model of the overlapping research areas (blue circles): exercise therapy as treatment for knee or hip pain, studies on the influence of the physical environment in hospital settings, and the concept of context effect, that this thesis (red dot) lies within.

3.1 Study design

The Ph.D. project protocol was externally peer-reviewed and approved by the Faculty of Health Science at University of Southern Denmark. The Regional Scientific Ethical Committee of Southern Denmark approved the trial (S-20130130), which was conducted in consistency with the Helsinki Declaration and registered at www.clinicaltrials.gov (ID: NCT02043613).

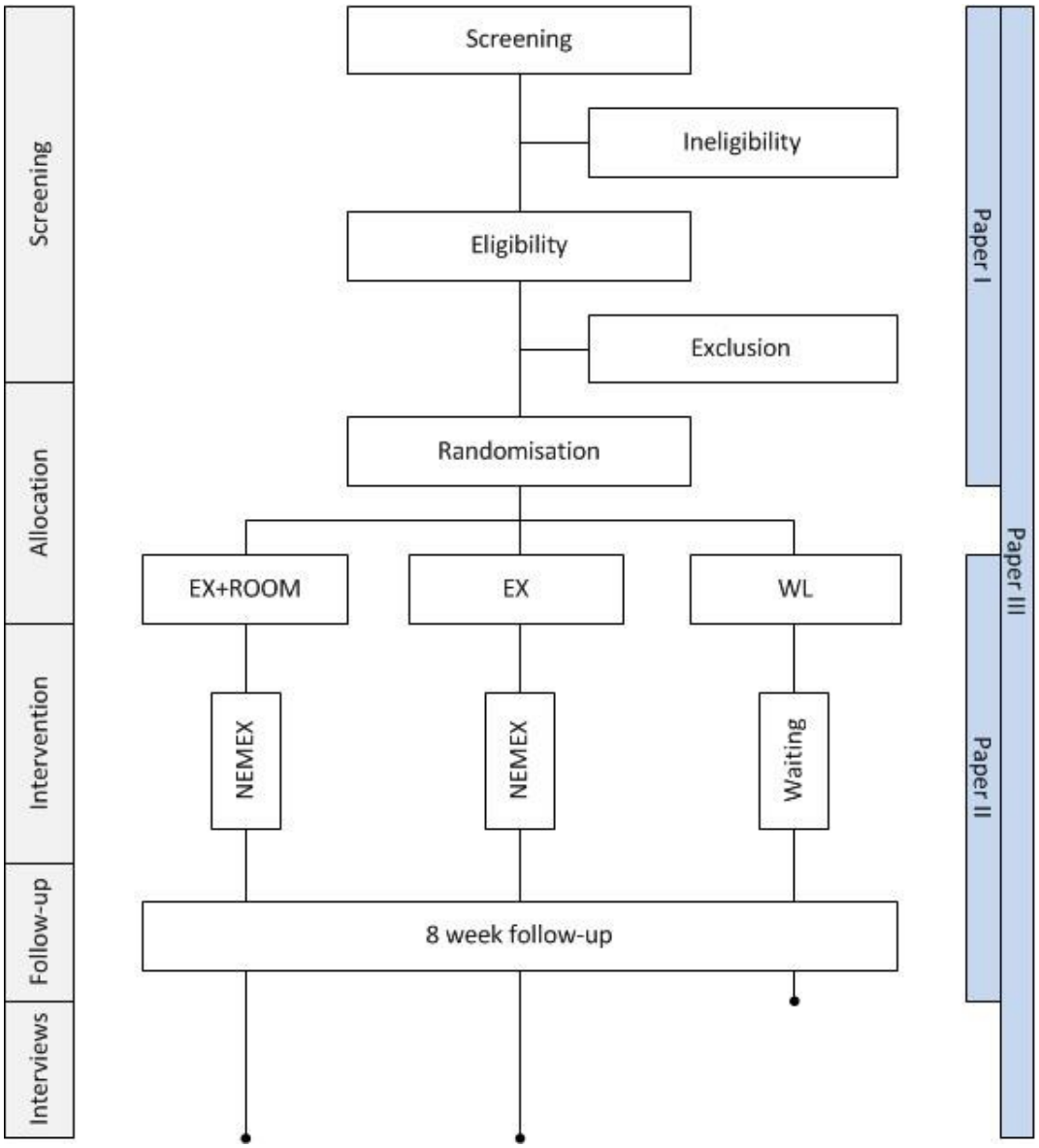


Figure 4: Schematic study design. On the left-hand side, the study phases are outlined; on the right-hand side, it is indicated which phases the included papers cover. EX+ROOM: intervention group exercising in the contextually enhanced environment, EX: intervention group exercising in the standard environment, WL, intervention group assigned to passive waiting list, NEMEX: neuromuscular exercise therapy program.

The trial was designed as a double-blind, three-armed, clinical RCT (Figure 4) to investigate the influence of the physical environment on the effect of exercise therapy by comparing exercise therapy performed in a contextually enhanced environment to a standard environment. The study hypothesis was that participants exercising in the contextually enhanced environment would report greater improvements than in the standard environment. The primary endpoint was participants' Global Perceived Effect (GPE) assessed on a 7-point Likert scale after completing eight weeks of neuromuscular exercise therapy.

3.2 Participants

3.2.1. Eligibility

Participants were eligible to enter the study if they met all inclusion criteria listed in Table 2. Participants were excluded from participation if they presented with any of the listed exclusion criteria.

Table 2: Eligibility criteria	
Inclusion	Exclusion
1) Age: 35 years or older 2) Self-reported persistent knee or hip pain within the past 3 months 3) Willing and able to attend exercise therapy at the University of Southern Denmark, Odense M	1) Co-morbidities or contraindications prohibiting exercise therapy 2) Inability to answer questionnaires or to speak, read, or understand Danish 3) Participation in exercise therapy, defined as supervised exercise or systematic training aimed specifically at relieving knee or hip problems with a duration of six weeks or more, started within the past three months 4) Surgery of the hip/knee within the past three months or awaiting joint surgery

No support was found in the literature that any particular population would be more susceptible to influence from the physical environment than other populations. Therefore middle-aged individuals with lower extremity joint pain were chosen as the study population for three reasons,

- Exercise therapy is a recommended first-line treatment for individuals with musculoskeletal pain (McAlindon et al. 2014).
- The prevalence of individuals with musculoskeletal pain is above 50% in the Danish population (Holmberg et al. 2015).
- The Research Unit for Musculoskeletal Function and Physiotherapy has extensive experience from trials on this patient group.

It is important to emphasize that the study population with musculoskeletal pain served as a model to investigate the influence of the physical environment on treatment response to in an exercise therapy setting. Any population treatable with exercise therapy could, in theory, have been chosen.

3.2.2. Recruitment

Recruitment for the study started in January 2014, with the first study participants enrolled in February. Inclusion was completed in November 2014 and the exercise intervention was completed in January 2015.

Participants were recruited in two ways: participant initiated contact via 1) posters and informational leaflets at general practitioners' offices and 2) via posters or articles in local newspapers, social media, or word of mouth. Participants were screened via telephone and, if eligible, they were sent written information about the trial and invited to a baseline visit. At the baseline visit, participants were verbally informed before giving their written consent to participate.

3.2.3. Randomisation

The randomisation was administered by a research secretary. Participants were randomised in a 2:2:1: allocation, immediately after their baseline assessment according to a computer-generated allocation list prepared by a statistician with no other involvement in the trial. Participants were consecutively assigned according to the list and given a numbered, sealed, opaque envelope entailing treatment allocation. Block randomisation was performed with each block consisting of either five or 10 participants. The randomisation was stratified according to primary site of pain, to avoid imbalance in treatment allocation.

3.2.4. Blinding procedure

Participants were blind to the overall study aim in order to avoid any excess focus on the physical environment that potentially would exaggerate the influence of the physical environment on treatment response. For the same reasons, the supervising therapists were blind to the overall study aim. Therapists supervised exercise sessions in both exercise environments and were consequently aware of the different locations. However, therapists were informed that this was due to logistic reasons. The primary investigator who performed all baseline and follow-up testing was aware of the overall aim, but blind to treatment allocation.

3.2.5. Ethical considerations

The primary ethical concern of this trial was the participants' blinding to the overall study aim. Therefore, participants were unaware that they would be randomised to exercise therapy in different physical environments. By withholding this information, participants were unable to assess the implication of the trial and whether they wanted to contribute to such research. However, it was

imperative that the focus on context effects remained implicit in order to give a true estimate of the influence of the physical environment on health outcomes and treatment response. However, participants were explicitly made aware of any risk factors or adverse events concerning participation in exercise therapy. The issues concerning blinding were carefully accounted for upon obtaining approval from the Regional Ethical Committee of Southern Denmark, which approved the study without any restrictions.

3.3 Intervention

Participants were randomly allocated to one of three groups:

1) Waiting list (WL)
2) Exercise in a standard environment (EX)
3) Exercise in a contextually enhanced environment (EX+ROOM)

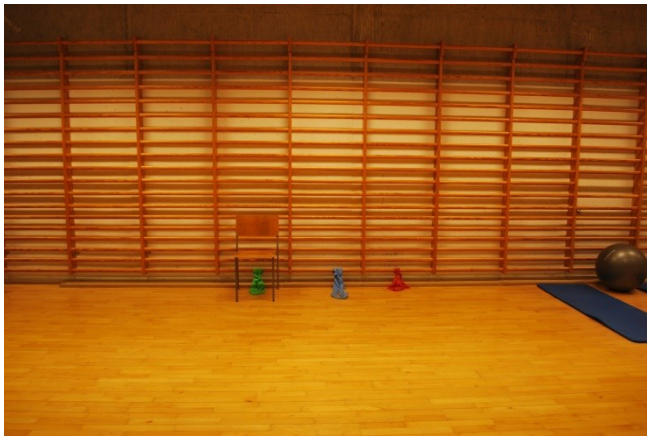
Group WL: waiting list

Participants randomised to the waiting list remained passive for the eight-week intervention period. Participants were instructed to maintain their lifestyle as up to inclusion into the trial during the intervention period. After completing the eight-week follow-up, participants on the waiting list were offered eight weeks of structured resistance exercise.

The waiting list was included as an untreated reference group to describe the natural disease progression of the study population (Kleijnen et al. 1994). This enables a comparison between untreated and treated participants (Di Blasi et al. 2003, Kaptchuk et al. 2008). Any difference between the untreated and treated participants will exclude the possibility that the observed treatment effect in the treated participants is caused by natural disease remission. This will be further elaborated on the in discussion section.

Group EX: exercise therapy in a standard environment

Participants randomised to this group exercised in a standard environment. This environment is marked by years of use and resembles many existing exercise facilities at hospitals and rehabilitation clinics. The room is located in the basement of an old university building and has no windows. It is accessed through a series of staircases and dark hallways. The room appears used with polished wooden floors, wall bars, and bare and unadorned concrete walls (Photograph 1-2).



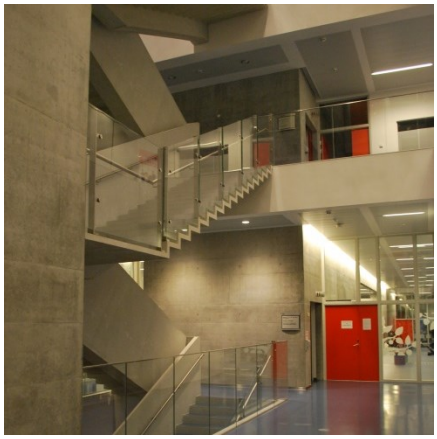
Photograph 1: Wall bars and exercise equipment in the standard environment

Photograph 2: Entry pathway into the standard environment

Group EX+ROOM: exercise in contextually enhanced environment

Participants randomised to this group exercised in a contextually enhanced environment. This environment is located on the first floor of a newly built university facility and has a view of an outdoor sport and recreational area. The room is designated for exercise therapy. It appears clean and new, with rubberized floors, smooth concrete walls, and new equipment (Photograph 3-4). Decorations included pictures of landscapes.

Photograph 3: Exercise equipment and view from the contextually enhanced environment



Photograph 4: Entry pathway into the contextually enhanced environment.

3.3.1. Factors within the physical environment

The two exercise environments were assessed on a number of factors to describe the exercise environments (Table 3).

Light intensity was quantified using a LUX meter (Amprobe, LM-100, light meter, Everett, WA, USA) on two representative positions in the exercise environments and directly at windows, if

present in the room (Walch et al. 2005). Light measurements were taken as close in time as possible to the exercise sessions.

Air quality was assessed using an air quality logger (Trotec, BZ-30, data logger, Heinsberg, Germany) collecting data every 30 seconds, thereby describing the CO_2 concentration, temperature, and air humidity in the environment during exercise.

Carefully selected pictures of nature scenes were mounted in the contextually enhanced exercise environment as additive to the vista of the recreational and sport area.

The acoustic properties speech interpretability, speech clarity, reverberation, and background noise were measured by use of standard acoustic methods (Kuttruff 2000). An acoustician performed these measurements before the intervention period started. Reverberation (T20) is descriptive of how well speech is perceived within a room. A long reverberation time affects speech comprehension negatively (Kuttruff 2000). Speech clarity (C50) compares early and late sound reflections within a room (Kuttruff 2000). Early sound reflections are perceived as clearer speech. Speech Transmission Index (STI) is a measure of sound quality in transmission of sound from source to receiver.

Table 3: Environmental factors within the exercise environments	Contextually enhanced environment	Standard environment
Building year	2012	1974
Patient satisfaction*, range 0-5, worst to best (95% CI) with:	(n=38)	(n=40)
Physical environment, p=0.00	3.9 (3.6 to 4.1)	3.4 (3.2 to 3.6)
Exercise therapy, p=0.45	4.3 (4.1 to 4.5)	4.4 (4.2 to 4.7)
Light (SD)		
Source	Daylight + artificial	Artificial
Strength (Lux)	2168 (744)	552 (39)
Air quality		
CO_2 (ppm)	eMethods, paper III	eMethods, paper III
Temperature (°C)	eMethods, paper III	eMethods, paper III
Humidity (%)	eMethods, paper III	eMethods, paper III
Interior		
Wall decorations (y/n)	y	n
Windows and view (y/n)	y	n
Music during exercise (y/n)	y	y
Acoustics (SD)		
Background noise (dB(A))	31.8 (3.9)	41.2 (2.4)
Speech Clarity Index (C50)	1.8 (1.3)	0.7 (0.8)
Speech Transmission Index (STI)	0.7 (0.0)	0.6 (0.0)
Reverberation (T20)	0.92	0.95
Interpretation from acoustician	Generally, all four acoustic measurements favour the contextually enhanced environment over the standard environment, but the differences were small. Regarding reverberation, the EX environment has higher numbers in the low frequency area, which will be perceived as echoing in the room.	

Table 3: *Satisfaction with room was a complied score of 9 single items, satisfaction with exercise was a complied score of 2 single items. Mean with 95% Confidence Intervals are presented. Higher numbers indicate greater satisfaction.
Ppm: parts per million, C50, clarity index with first 50 msec of sound (mean across frequencies from 250Hz to 8kHz), STI: speech interpretability index, T20: reverberation time for sound decay of 20 dB (from 400Hz-1,25kHz). SD; Standard Deviation. *Table from paper III*

3.3.2. Exercise therapy (Papers II and III)

The exercise therapy programme for participants in both exercise groups (EX+ROOM and EX) was based on the standardised NEuroMuscular EXercise (NEMEX) programme (Ageberg et al. 2010). The NEMEX programme has been examined for feasibility and previously been shown effective for relieving pain and improving function in a variety of populations with knee or hip pain (Zätterström

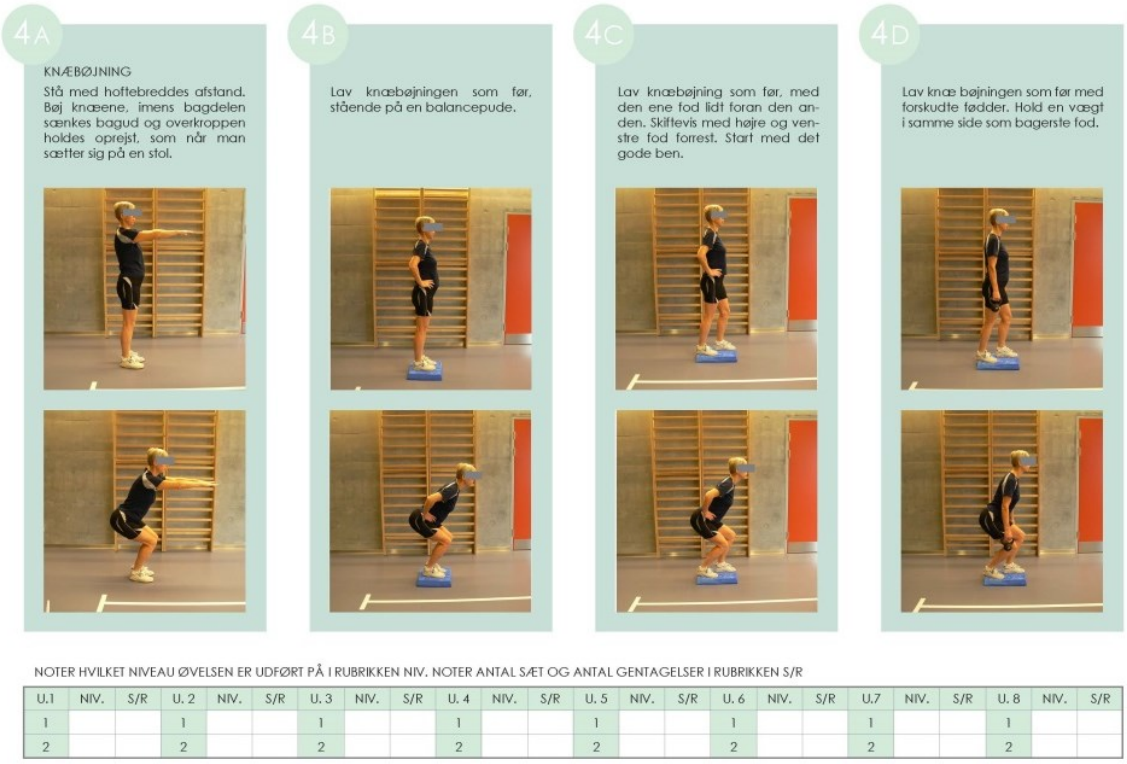
et al. 1992, Zätterström et al. 1998, Roos et al. 2005, Ericsson et al. 2009, Ageberg et al. 2013, Villadsen et al. 2013). The NEMEX programme is based on biomechanical and neuromuscular principles and aims to improve sensorimotor control and achieve functional stability in daily movements (Ageberg et al. 2010). The exercise programme consisted of 11 specific exercises each with four progression levels. The programme consisted of three elements: a warm-up on an ergometer bike, a circuit programme, and a cooling-down period (Ageberg et al. 2010). The circuit programme included exercises focusing on lower extremity muscle strength, postural function, postural orientation, and function of the lower extremity during daily tasks (Ageberg et al. 2010). Exercises were performed bilaterally in two to three sets with 10-15 repetitions (Ageberg et al. 2010). The cooling down period included passive muscle stretching and a mobility exercise for participants with hip pain as primary complaint.

The exercise therapy was performed as group-based exercise, supervised by therapists certified to deliver the NEMEX programme. Therapists were certified by attending a two-day course with the Good Life with Osteoarthritis in Denmark programme (www.glaid.dk). The course focused on lower-limb OA management and neuromuscular exercise therapy. Additionally, all therapists practiced supervising the exercises with the primary investigator to ensure consistency in supervision of participants regarding how and when to adjust volume, load, and progression of each exercise. Both exercise groups exercised on Tuesday and Thursday afternoons, each exercise session had duration of one hour. Therapists first supervised in the contextually enhanced environment and thereafter in the standard environment. Consequently, all therapists involved in the study supervised exercise therapy in both environments and for the same amount of time. This setup was chosen to ensure that any influence from specific therapists would be similar across environments, thereby standardising therapist characteristics and participant-therapist relationships.

Exercise dairies (Paper II)

Participants self-reported joint pain using an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) (Hawker et al. 2011). This was done to monitor participants' tolerance to the exercise therapy programme and progression level of the specific exercises. Participants recorded their joint pain and exercise levels and volume in a personal exercise diary, stored in the respective exercise environments, before and after every attended session (Figure 5). Joint pain was accepted during exercise and could, according to two rules regarding level of pain and duration of increased pain, be used to guide progression or regression within the eight-week period (Ageberg et al. 2010). Pain within the 0-2 interval on the 11-point scale was considered safe, pain in

the 3-5 interval was acceptable, whereas pain above 5 was categorized as high-risk. If reporting pain above 5, then the exercise volume or level would be adjusted to suit the participant at the next exercise session (Ageberg et al. 2010).



U.1	NIV.	S/R	U. 2	NIV.	S/R	U. 3	NIV.	S/R	U. 4	NIV.	S/R	U. 5	NIV.	S/R	U. 6	NIV.	S/R	U.7	NIV.	S/R	U. 8	NIV.	S/R
1			1			1			1			1			1			1			1		
2			2			2			2			2			2			2			2		

Figure 5: Example from the exercise diary. Each participant had their own exercise diary. On the front page they registered pre- and post-exercise pain. On the following pages, illustrative pictures of the exercises were shown, including the four progression levels possible. Participants noted their current progression level and number of sets and repetitions at each attended exercise session.

Compliance and adverse events (Papers II and III)

Compliance with exercise therapy was recorded as attendance to exercise sessions. Compliance was considered good when participants attended 12 or more of the 16 possible exercise sessions. Participants in the waiting list group were asked at the eight-week follow-up if they had started any exercise routines within the eight–week intervention period. If answering yes, participants were asked to describe this change.

Participants self-reported adverse events experienced in between exercise sessions in an online survey at four and eight weeks. Adverse events were defined as events restricting them physically, mentally, or socially. Participants also indicated whether they had been in contact with

either their general practitioner or the hospital in relation to any adverse event. Adverse events occurring during the exercise sessions were recorded by the supervising therapists.

3.4 Outcomes

3.4.1. Primary outcome

The primary outcome of the RCT was participants' GPE assessed at the eight-week follow-up (Figure 6). Participants were asked to respond on a 7-point Likert scale to the following question: *"Compared to before you entered the study, how are your knee/hip problems now?"* The scale ranged from [-3] "markedly worse" through [0] "no change" to [3] "markedly improved." GPE is a reliable effect measure in clinical trials and for individuals with musculoskeletal disorders (Guyatt et al. 2002, Kamper et al. 2009, Kamper et al. 2010). The validity of GPE scales have been questioned and criticised since ratings on transition scales are strongly influenced by the patients' current state when rating their transition (Kamper et al. 2010). However, one study showed a correlation of 0.8 between the change score of a quality-of-life questionnaire and a transition rating (Guyatt et al. 2002). This suggests that a transition scale, such as the GPE, is valid for detecting changes and can be used in clinical trials as primary outcome measures (Guyatt et al. 2002).

□	□	□	□	□	□	□
Markedly worse	Somewhat Worse	Slightly worse	No change	Slightly Improved	Somewhat improved	Markedly improved

Figure 6: Primary endpoint. A 7-point Likert scale was used to rate the participants' global perceived effect at the eight-week follow-up visit.

3.4.2. Secondary outcomes

All patient-reported outcomes were collected using an online survey at baseline, four weeks and eight weeks. Objectively assessed outcomes were collected at baseline and eight weeks (Table 4).

Table 4: Outcomes	Paper II	Paper III
Participants' Global Perceived Effect		√
Patient-reported outcomes		
KOOS		√
HOOS		√
SF-36		√
ASES		√
Stress level		√
Joint pain, index joint	√	
Exercise-induced pain (collected pre and post exercise sessions)	√	
Objectively assessed outcomes		
Knee bends/30 seconds		√
Chair stand/30 seconds		√
One-leg hop for distance		√
Single limb mini-squat		√
Walking test, fast-paced, 4*10 m		√
Aerobic capacity		√
Isometric strength, knee extension		√
Isometric strength, hip abduction		√

Table 4: KOOS; Knee injury and Osteoarthritis Outcome Score, HOOS; Hip disability and Osteoarthritis Outcome Score, SF-36; Short-Form Health Survey (36 items), ASES, Arthritis Self-Efficacy Scale.

Patient-reported outcomes

The joint-specific questionnaires The Knee injury and Osteoarthritis Outcome Score (KOOS) and The Hip disability and Osteoarthritis Outcome Score (HOOS) were used for participants reporting their knee or hip as index joint, respectively. KOOS/HOOS assesses pain, symptoms, activities of daily life function, sport and recreational function, and joint related quality of life in five separate subscales (Roos et al. 1998, Nilsdotter et al. 2003). KOOS and HOOS have good psychometric properties for patient groups with knee injury, knee replacement, hip dysfunction and hip replacement (Roos et al. 1998, Roos et al. 1998, Klassbo et al. 2003, Nilsdotter et al. 2003, Roos et al. 2003).

The Medical Outcome Study 36-item short form general health survey (SF-36) was included as a generic health measure (Ware et al. 1992, Mchorney et al. 1993, Mchorney et al. 1994). It assesses general health and aspects of physical and mental functioning and limitations. It includes eight

separate subscales, that can be combined in a physical and mental component score, respectively (Ware et al. 1992). The validity and reliability of the SF-36 has previously been reported (Mchorney et al. 1993, Mchorney et al. 1994).

A modified version of the Arthritis Self-Efficacy Scale (ASES), entailing the pain and symptoms subscales, was included to evaluate participants' perception of their knee or hip joint functionality (Lorig et al. 1989).

Additionally, participants' satisfaction level with 1) the exercise therapy intervention itself, and 2) specific contextual factors within the respective physical environments was assessed using adapted items from Tsai et al. (Tsai et al. 2007). Satisfaction was scored on a 5-point Likert scale ranging from 1 to 5 (1=strongly dissatisfied, 2=dissatisfied, 3=fair, 4=satisfied, and 5=strongly satisfied). General stress level was measured on a 100 mm visual analogue scale ranging from no stress to stress as severe as possible (Kweon et al. 2008, Lesage et al. 2011).

Objectively assessed outcomes

As the study encompassed a population with a large variation in age, pain severity and physical function, a variety of functional performance tests of varying difficulty were included to ensure all participants would be challenged.

Single-limb mini squat | Knee bend test | Chair stand test | One-leg hop for distance | 4*10 m walking test

*Figure 7: Functional performance tests. From the left-hand side: 1) single-limb mini squat assessing knee position during knee bending, 2) knee bend test, assessing number of knee bends during 30 seconds, 3) chair stand test assessing number of rises from a chair during 30 seconds, 4) one-leg hop for distance test, and 5) 4*10m fast-paced walking test assessing walking speed.*

Functional performance was assessed by five performance tests (Figure 7). The single limb mini squat test assessed movement quality during semi-squatting on one leg (Ageberg et al. 2010). The number of knee bends performed on one leg during 30 seconds (Bremander et al. 2007, Thorlund et al. 2010),

number of chair stands during 30 seconds (Dobson et al. 2012, Dobson et al. 2013), a one-leg hop for distance test (Bremander et al. 2007) and a 4*10 m fast-paced walking test assessing walking speed (Dobson et al. 2012). All functional performance tests provide valid assessment of lower extremity function in different patient groups with knee or hip problems (Bremander et al. 2007, Gill et al. 2008, Wright et al. 2011, Dobson et al. 2013). The included chair stand test and fast-paced walking test are recommended tests to assess function in knee and hip OA populations (Dobson et al. 2013).

Maximal isometric knee extension and hip abduction strength were evaluated using dynamometry (JTECH medical, Commander Echo, Salt Lake City, Utah, USA) using an adapted method from (Thorborg et al. 2013). Aerobic capacity was estimated from work load and stabile heart rate during a submaximal work rate bicycle test (Astrand et al. 1954).

3.5 Nested qualitative study

A qualitative interview study was nested within the RCT to investigate participants' and therapists' perceptions and experiences of the respective exercise environments. It entailed semi-structured focus-group interviews with participants from the two environments separately and individual one-to-one interviews with the supervising therapists. The combination of quantitative and qualitative data will help illustrate and elaborate on the complexity of context effects (O'Cathain et al. 2013).

3.5.1. Recruitment, sampling and consent

After completing their eight-week follow-up visit participants were verbally invited to participate in a focus group interview to share their experiences and thoughts about the exercise programme. Sampling for the interviews was based on availability and was therefore a convenience sample drawn from the study population (Ritchie et al. 2014). If willing to attend interviews, participants were given possible time and dates of interviews and they then replied back via email the date that suited them best. Participants were sent an email three to four days in advance of the interview as a reminder. This email also had instructions on how to cancel if participants had reconsidered. The data collection for the nested qualitative study was performed from December 2014 to March 2015. A principle of maximal variation was applied in order to compose heterogeneous focus groups in relation to age, gender, and site of primary pain (Finch et al. 2014). Focus-groups included between three and five participants. The flow of participants attending interviews is described in Figure 8.

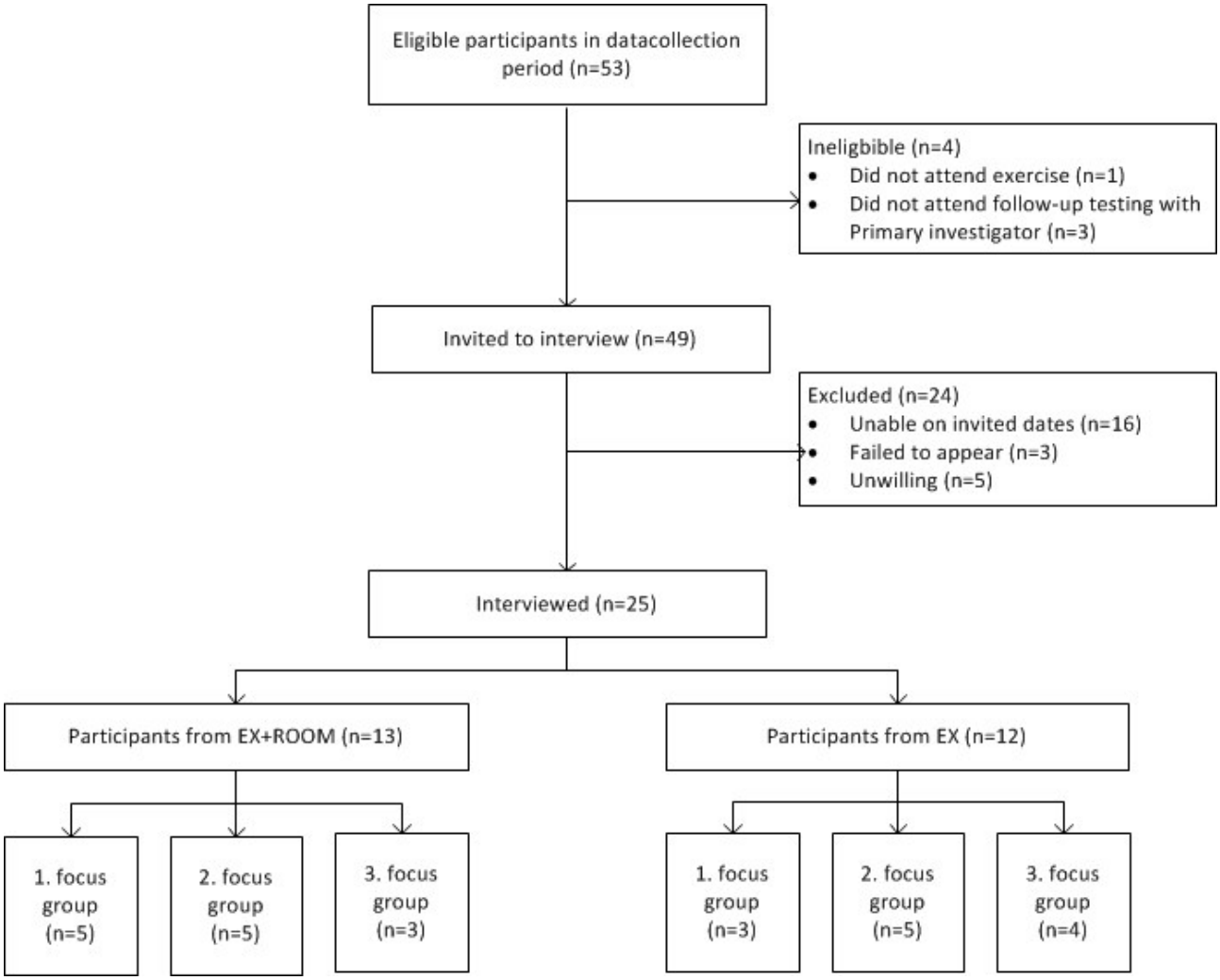


Figure 8: Flow of participants eligible, invited, and interviewed participants in the nested qualitative study. EX+ROOM: contextually enhanced environment, EX: standard environment.

The three therapists supervising the exercise therapy during the latter part of the intervention period (August-December 2014) were invited to an individual one-to-one interview; two therapists accepted. Therapist interviews were conducted to capture the variation and potential difference between performing (participant) and supervising (therapist) exercise therapy in the two exercise environments.

Prior to the interviews, participants and therapists were given written and verbal information regarding the focus of the interviews. Hereafter, they confirmed their willingness to participate and gave their written consent. All focus group interviews were conducted after the participants had completed their eight-week follow-up visit and therapists were interviewed after the intervention period had ended. This was done in order to maintain blinding to study aim at time of final follow-up.

3.5.2. Data collection methods

Focus group interviews

Focus group interviews were conducted with participants from the two different environments separately, to ensure that the participants' frame of reference remained consistent within the focus groups. Focus group interviews are useful to explore people's knowledge and experiences and to examine not only *what* people think but also *how* and *why* they think that way (Kitzinger 1995). In the focus-group interviews, participants could refine their statements through discussions and reflect upon agreements and disagreements with other participants (Finch et al. 2014).

A topic guide was developed prior to the focus group interviews in collaboration with the research team. It was underpinned by theoretical literature on context effects in health-care (Di Blasi et al. 2001, Moerman et al. 2002, Di Blasi et al. 2003, Miller et al. 2008), therapeutic landscapes (Williams 1998, Gesler 2003, Gesler 2005) and notions from humanistic geography (Seamon 1980). Questions were organised in such a way as to first address the participants' general experience of the exercise therapy, before moving on to their experience of the environment. The topic guide was tested in a pilot focus group and modified to ensure clarity of questions and to adjust the sequence of questions. The primary investigator acted as moderator for the focus-group interviews while a research secretary recorded the sequence of participation and took notes about participants' non-verbal responses during the interview. All interviews were audio recorded.

When attending the interviews, participants were still blind to the overall study aim. At no point did the interviewer explicitly state the overall study aim to the participants. After the general questions of the topic guide, the moderator explained that in addition to gaining knowledge about the general experience, the interviews also aimed to explore participants' thoughts about the physical environment. This was accepted by participants in all interviews without questions or disbelief.

Individual interviews

A single one-to-one interview with each therapist focussed on their perception and experience of supervising exercise therapy within the different environments. A similar topic guide was used as for the focus group interviews, though the wording was adapted to suit the therapists' perspective. Additional questions were included to explore whether the therapists had observed any difference in participants' behaviour and group dynamics between the two environments.

When therapists attended their interview, they were blind to the overall study aim. However, after completing the general questions of the topic guide, the moderator told the therapists that in

addition to investigating the effect of exercise, the study investigated the influence of the physical environment on the effect of exercise. The unblinding of the therapists did not result in any concerns or feelings of being misled in the therapists.

Photo elicitation

A photo-elicitation technique was used in interviews, which entailed using photographs as interview stimuli to evoke deeper elements of human consciousness (Harper 2002). Studies using the photo-elicitation technique report that informants give deeper, richer responses and that the images also evoke emotional responses (Pain 2012). Previous research has found this technique to be effective when exploring people's perception of spaces and places within healthcare (Radley et al. 2003, Radley et al. 2003, Moore et al. 2013). Consequently, photographs of different elements of the exercise environments were used to prompt responses from the participants during interviews. Photographs were taken by the researcher from the point of view that participants would have had during the exercise sessions (examples of photographs used in the interviews, see Photographs 1-6, all pictures in eMethods for paper III). Additionally, the exercise environments were set out with exercise equipment as it was during the exercise sessions. Eight photographs from each exercise environment were chosen. In the focus group interviews, participants were shown photographs only from the environment in which they had exercised. During the individual interviews with therapists, photographs from both exercise environments were shown.

3.5.3 Data analysis

Interviews were transcribed verbatim and anonymised. Interviews were analysed using the Framework approach (Smith et al. 2011, Gale et al. 2013, Spencer et al. 2014). Analysis started with familiarisation of the transcripts through listening to the audio recordings, transcribing, and re-reading transcripts. Transcripts were coded thematically using both deductive (pre-specified codes informed by the literature) and inductive (codes drawn from the text) codes. To ensure rigor, two transcripts were independently double-coded by two experienced qualitative researchers. An initial coding framework was developed, discussed, refined, and then reapplied systematically to the transcripts. Each analytical code was then organised into a matrix, and then summarised in cells with columns representing codes and rows representing a case (either a participant or therapist) (Figure 9) (Spencer et al. 2014). The matrix allowed a comparison of the data within and across the interviews and provided a visual map of the data. Developments within the matrix were regularly discussed with the experienced researchers supervising the analysis. As a result of this iterative

process of discussing and revising the coding and framework matrix, codes were—based on their content or concepts discussed in the codes—grouped together under overarching themes most predominant in the transcripts.

	A : Atmosphere	B : Body perception	C : Caring
19 : C2_Janni	Had a specific feeling that this exercise is what I need to do, came from the exercise and the physio, didn't relate to basement.	Unhappy with own body, overweight feeling ashamed because of overweight. Didn't want to humiliate her self, if there was things she couldn't do, but felt that everyone respected her limitations. Proud and happy to rediscover body. cries when she tells the group.	felt taken care of, but not carried/patronized (by instructor) boundries of physical ability were respected by everyone didn't feel judged by other participants. was glad to be helped and appreciated instructors adapting exercises individually.
20 : C2_Rene	People were dedicated/committed to the exercise/project. People went at it, despite pain.	Depressing - Narativ: comparing disabled body with gymnasts body. limping home (LFS, joking, but he is really frustrated with his own limitations)	felt safe, because the instructor was there to help, all the time.
21 : C2_Tina	fantastic atmosphere, motivating felt comfortable, safe the atmosphere was contagious, that was motivating. Good atmosphere, being social, talking, the instructors.	Humble, afraid of taking someones place hadn't observed own knees before, opportunity to use mirrors as tool.	N/D

Figure 9: Example of the analytical matrix used in the Framework analysis (NVivo 10, software). Columns represent the analytical codes and rows represent a case (either a participant or therapist). The thoughts and statements regarding an analytical code were summarised in cells for each participant or therapist, the pink shading represents links to citations within the interview transcripts.

3.6 Sample size estimation and power considerations

Since no previous studies were identified investigating the influence of the physical environment on the effect of exercise therapy as treatment for knee or hip pain, no previous data were available on which to base sample size estimations. Thus, the power calculation was based on factors such as feasibility and pragmatic issues such as access and capacity of the exercise environments. Taking these aspects into consideration, the study sample was set at 100 participants. Randomisation was performed with a 2:2:1 allocation and thus 40 participants were randomised to each of the exercise environments and 20 participants to the waiting list group. A limited treatment effect was anticipated in the waiting list group. Therefore, the number of participants in this group was

reduced. With 40 participants in each of the two exercise environments (EX+ROOM and EX), the trial would be able to detect a significant difference of 0.75 on the 7-point GPE scale assuming a standard deviation of 1.2, a significance level of 0.05, and a power of 80%.

3.7 Statistical evaluation

Paper II:

A Student's paired t-test was used to compare difference in joint pain from baseline to eight weeks follow-up for participants randomised to exercise. To investigate the influence of compliance on pain relief from exercise therapy, an unpaired Student's t-test was performed to test for any difference in change in pain from baseline to follow-up between the compliant (at least 12 sessions) and non-compliant (less than 12 sessions) groups.

Pain ratings from the 16 individual exercise sessions were used in the pain trajectory analysis. Linear regression analysis was performed to investigate pain trajectory over time, using the group mean pre-exercise pain ratings from each individual exercise session as dependent variable and time as independent variable. Similarly, linear regression was performed to investigate the size of acute pain flare evoked by the individual exercise session. The group mean difference in pain between the before- and after-exercise pain assessments for each of the 16 exercise sessions was the dependent variable and time was the independent variable. P-values of <0.05 were considered statistically significant.

Paper III:

A statistical analysis plan was completed and made publicly available on the university website prior to conducting data analysis (Sandal et al. 2015). To further minimise the risk for bias introduced during analysis and interpretation, data analysis of the primary outcome was performed by a third party not related to the study. The third party was given data with intervention groups allocated with arbitrary names. Interpretation was then performed by the primary investigator in collaboration with the research team prior to revealing treatment allocation, thereby the results were interpreted with the research team blinded to group allocation (Jarvinen et al. 2014). As suggested, all co-authors agreed in writing two alternative interpretation scenarios prior to breaking the randomization code (Jarvinen et al. 2014). Consequently, two interpretations were drafted on the basis of the primary outcome data. One scenario assumed that group A was the group exercising in the contextually enhanced environment and the other scenario assumed that A was the group exercising in the standard environment.

All three groups (EX+ROOM, EX and WL) were examined for comparability at baseline with respect to demographic factors using analysis of variance and Chi-squared test, as appropriate. The primary analysis was a Student's unpaired t-test comparing GPE scores between the contextually enhanced environment and standard environment at the eight-week follow-up. The waiting list group was considered a reference group describing the natural disease remission for the study population and was not included in the primary analysis. Secondly, a linear test for trend was performed across all three groups to explore the a priori hypothesis of a graded relationship between groups; waiting list < standard environment < contextually enhanced environment. An a priori defined per-protocol analysis was performed including participants attending at least 12 of 16 possible exercise sessions. Secondary analyses of the patient-reported outcomes and functional performance tests were performed using repeated measures and a multilevel mixed-effect model with participants as random effect, time, group, and interaction between time and group as fixed effects. In similarity with analysis of the primary outcome, only the exercise groups were compared. All available data points (baseline, four and eight weeks) were included.

4 SUMMARY OF RESULTS

The flow of participants in the RCT is illustrated in Figure 10. In total, 290 participants were screened for eligibility; of these 103 participants were eligible and willing to undergo randomisation. Participants were randomised to the three intervention groups in a 2:2:1 allocation; 42 participants exercised in the contextually enhanced environment, 40 exercised in the standard environment and 21 were on the waiting list. One participant from the waiting list withdrew consent after being randomised and one participant exercising in the contextually enhanced environment declined to participate in the eight-week follow-up (Figure 10).

4.1 Participants

The baseline characteristics of the included participants are given in Table 5 and the group of participants included for the different papers are indicated.

Table 5: Participants' baseline characteristic	Paper II	Paper III			
Group	NEMEX n=78	EX+ROOM, n=42	EX, n=40	WL, n=21	p-value*
Age (years), mean (SD)	58.6 (10.4)	59.6 (10.9)	57.6 (9.8)	58.2 (7.9)	0.65
Women, n, (%)	46 (59%)	25 (60%)	25 (63%)	13 (62%)	0.96
BMI, mean (SD)	28.1 (5.3)	28.4 (5.0)	28.0 (5.8)	29.1 (7.0)	0.79
Medical comorbidities, participant median pr. group, n,	2	2	1	2	0.28
Index joint, knee (%)	49 (63%)	26 (62%)	26 (65%)	13 (62%)	0.95
Pain index joint, NRS, mean (SD)	3.7 (2.1)	3.9 (2.0)	3.6 (2.2)	4.1 (2.4)	0.57
Clinical OA diagnosis, n, (%)	46 (59%)	22 (52%)	26 (65%)	13 (62%)	0.48
Pain duration, n, (%)					
0-6 months	4 (5%)	1 (2%)	3 (7.5%)	0 (0%)	
6-12 months	7 (9%)	4 (10%)	3 (7.5%)	1 (5%)	
1-5 years	32 (41%)	20 (48%)	14 (35%)	11 (52%)	
< 5 years	35 (45%)	17 (40%)	20 (50%)	9 (43%)	0.61

Table 5: SD, Standard Deviation, BMI, Body Mass Index, OA, osteoarthritis, NRS, Numerical Rating Scale ranging from 0 - 10. Medical comorbidities are given as median for the group; comorbidities include heart disease, elevated blood pressure, lung disease, diabetes, ulcer, kidney or liver disease, anaemia, cancer, depression, arthritis, lower back problems, rheumatic disease, and other self-reported medical comorbidities.
*p-values indicate the comparability of the three intervention groups at baseline in paper III.

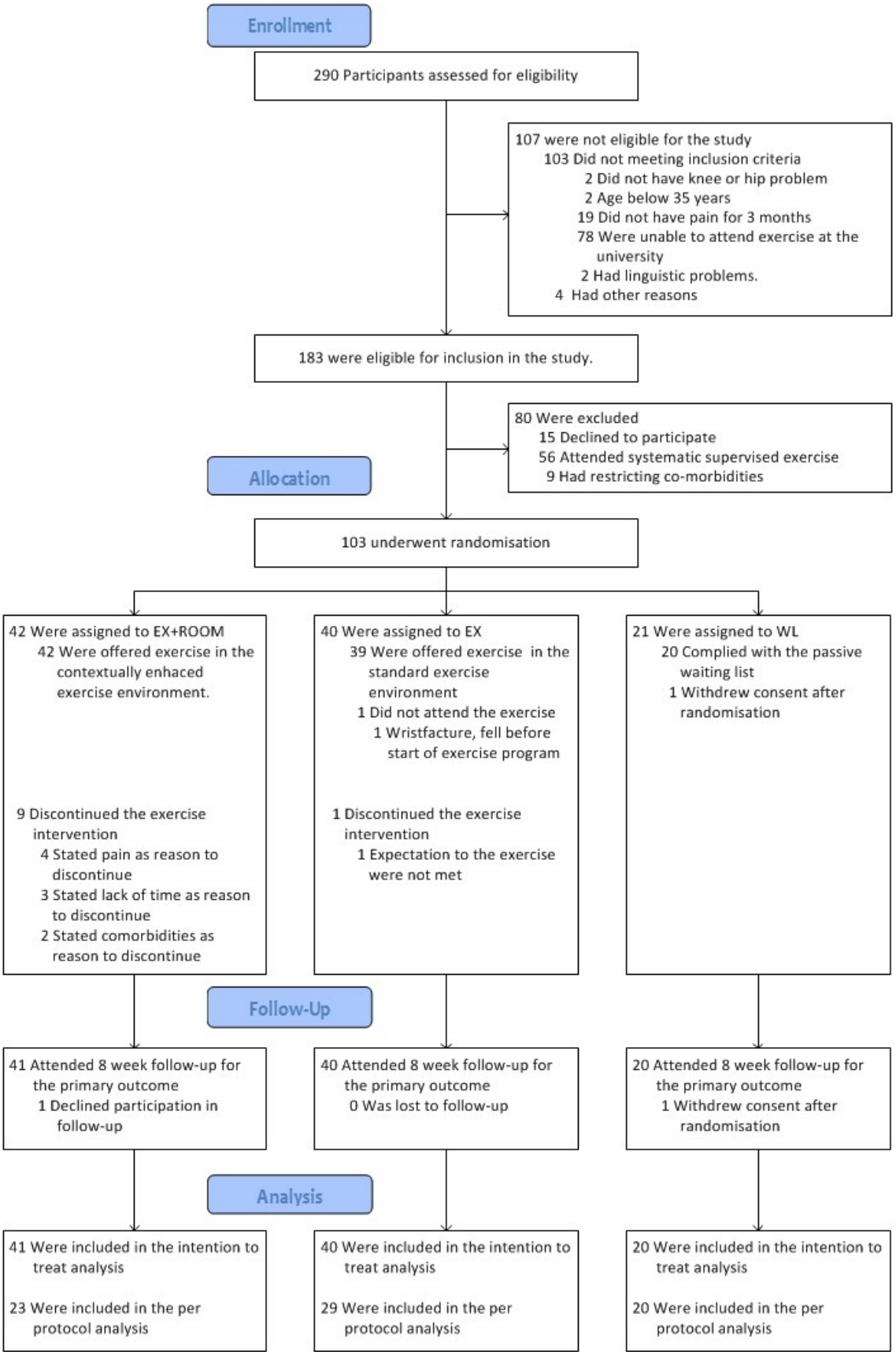


Figure 10: Flow chart for RCT study; enrolment, allocation, intervention, follow-up and analysis. Figure from paper III.

4.2 Influence from the physical environment on exercise therapy (Paper III)

4.2.1. Participants' global perceived effect

The waiting list reported no improvement (-0.05 GPE CI 95% -0.5 to 0.4) and when compared to the exercise groups combined, participants who exercised had greater treatment response than the waiting list group (0.67 GPE CI95% 0.33 to 1.00), p=0.05. Contrary to the study hypothesis, participants who exercised in the standard environment reported greater treatment response (0.98, CI 95% 0.5 to 1.4) compared to participants who exercised in the contextually enhanced environment (0.37, CI 95% -0.2 to 0.9), p=0.07. When examining the three intervention groups in the a-priori hypothesized order (waiting list < standard environment < contextually enhanced environment), no significant trend across the groups was found, p=0.36.

For the per-protocol analysis including participants with good compliance to exercise therapy (i.e. attending at least 12 of 16 sessions), the treatment response was greater in both exercise groups (standard environment 1.3, CI 95% 0.9 to 1.7, contextually enhanced environment 0.8 CI 95% 0.3 to 1.4, difference between EX+ROOM and EX groups p=0.20), indicating a positive relation between dose of exercise and treatment response. Similar to the primary analysis, the per-protocol analysis favoured the standard environment over the contextually enhanced environment.

4.2.2. Secondary outcomes

Patient-reported outcomes evaluating symptoms, function, and quality of life related to the joint and self-efficacy supported the primary finding of greater treatment response in the standard environment (Figure 11). However, there was no difference in the objectively assessed outcomes aerobic capacity, knee extensor or hip abduction muscle strength between the two different environments. For the functional performance tests, only improvement in the knee bend test was significantly greater for participants from the standard environment, where participants on average performed 3.2 knee bends more after the exercise period, compared to no change in participants from the contextually enhanced environment, p=0.05. The primary and secondary outcomes are summarized in Figure 11 (group means and difference can be seen in eTable1, paper III).

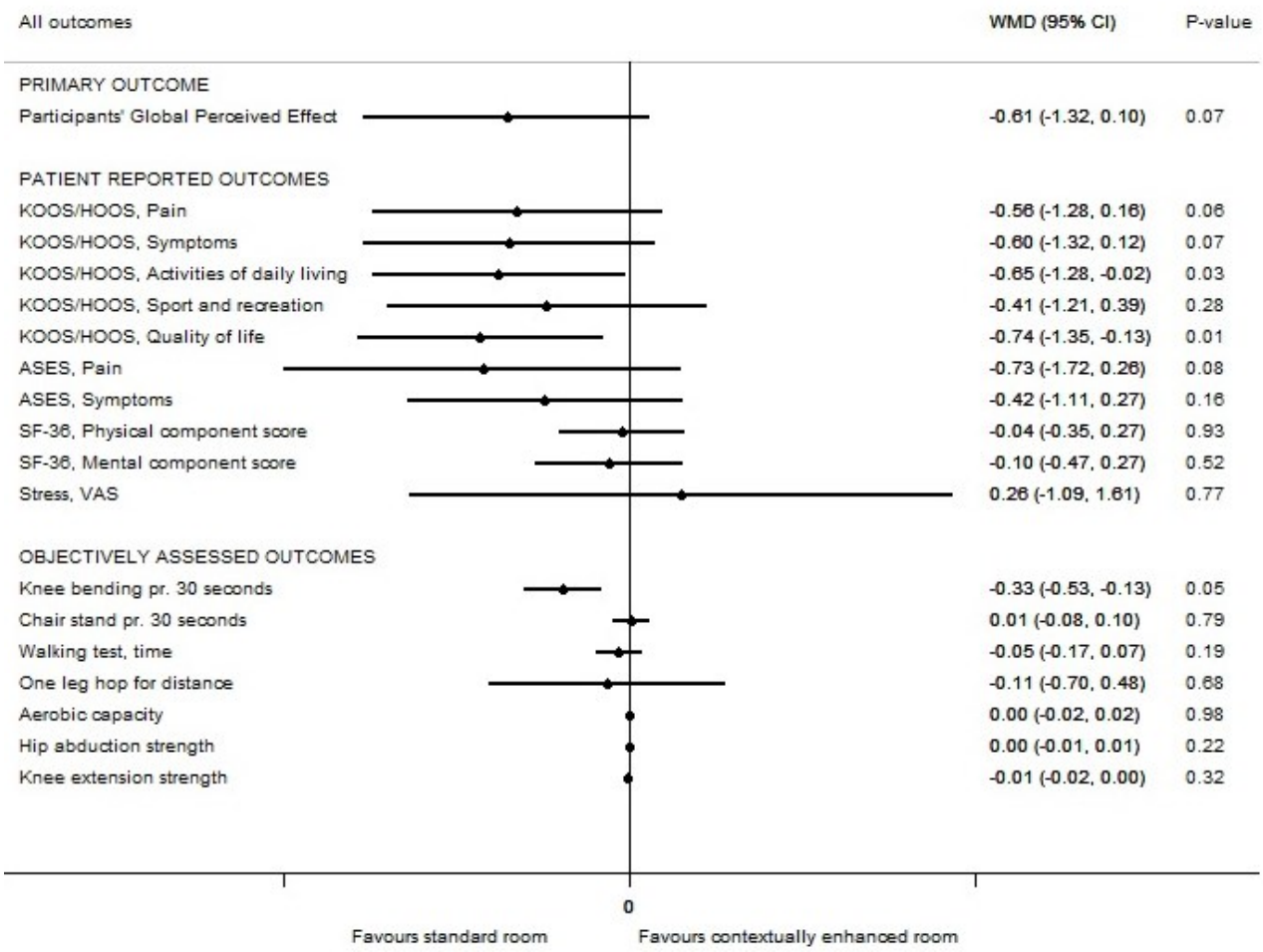


Figure 11: Mean difference in treatment response on primary and all secondary outcomes from eight weeks of exercise between the standard environment and the contextually enhanced environment. Estimates to the left of the 0-line favour the group exercising in the standard environment, outcomes to the right of the 0-line favour the group exercising in the contextually enhanced environment. Confidence intervals crossing the 0-line indicate the difference in treatment response not being statistically significant. KOOS; Knee injury and Osteoarthritis Outcome Score, HOOS; Hip disability and Osteoarthritis Outcome Score, ASES; Arthritis Self-Efficacy Scale, SF-36, Short Form Health Survey 36 items, VAS; visual analogue scale, 100 mm, WMD; weighted mean difference, 95% CI; 95 % confidence intervals. All secondary outcomes were scaled in an 1:10 ratio in order to ensure comparable visual proportions across outcomes with scales of different range. Figure from paper III.

The number of self-reported adverse events was low for all groups and no differences were seen between groups. The most commonly self-reported adverse event was transient exercise-induced pain flares, up to 26% of participants from the contextually enhanced environment and 18% in the standard environment reported transient pain flares with exercise therapy (see eTable2 in paper III). There were no reports of adverse events recorded by the therapists during the individual exercise sessions.

4.3 Qualitative findings (Paper III)

The qualitative interviews provided insight into how participants experienced and reflected upon their experiences from their respective exercise environments. The major themes that emerged during the framework analysis were: 1) Reflection—how features of the physical environment facilitated participants to reflect upon their physical body and identity within the environment; 2) transition—participants' experiences of entering the exercise environments and how this experience changed with time; and 3) sense of fellowship—how participants described their relationships with each other and how those relationships were influenced by the physical environment.

4.3.1 Reflections

Elements within both exercise environments caused participants to reflect on their physical bodies and their sense of identity. In both environments, mirrors were purposefully placed in the rooms to provide participants with visual feedback to improve the quality of their movement when performing exercises (Photograph 5-6). For example, participants could ensure that the hip, knee, and foot were well aligned while walking up or down a step. The mirrors presented participants with a direct reflection of their own body. However, participants felt uncomfortable seeing a reflection of their body when exercising and consequently avoided the mirrors. When the therapists explained the purpose of the mirrors and motivated their use, participants accepted the mirrors more readily as a tool.

> *Mikkel:*
> *Well, to start with, participants were a bit hesitant to go in front of the mirrors. […] But I kept telling them that it was because they then could see what they were doing and help themselves, and then they got used to it. (Therapist interview)*

Photograph 5: Mirrored wall in the contextually enhanced environment

Photograph 6: Mirrors in the standard environment

Participants associated the mirrors with commercial gym facilities, an exercise environment which participants thought to be inappropriate for exercise therapy. Commercial gym facilities were associated with having large mirrored walls on more than one wall surface. Participants feared that if more mirrors had been present in the exercise environments, as in commercial gym facilities, then they would be constantly confronted with their own body image from all angles. Participants also worried that others would potentially be observing them in the mirrors. Participants felt the surface covered by mirrors in the two exercise environments was suitable, as they could choose when to use the mirror as a feedback tool and when to move away from the mirrors.

> *Hanne:*
> *Well, it is the mirrors. I have a phobia of mirrors. […] It's because you do not care much about your own appearance, I think. [...] Then it isn't nice to go to a commercial gym, where there are mirrors all around, really. You can't close your eyes, so you have to look at the instructor, but she's a bit more fit than you, right. […] But in this exercise room I decided. I could go over to use the mirrors if I wanted to, and I could say to myself, "you know what, I came here simply to exercise my knee". (Focus group (FG) 3, standard environment)*

Participants from the standard environment felt a symbolic reflection as they perceived the worn, older features of the room as a reflection of their own physical state. This symbolic reflection was not perceived in a negative way; rather, they identified themselves with the environment as they felt they fitted better with the environment. Participants from the standard environment reported feeling more at-home, compared to those from the contextually enhanced environment, who expressed neither a feeling of being at-home nor a feeling of being uncomfortable within their environment.

> *Mia:*
> *I actually liked it better here (than in a commercial gym). […] It was like we set the standard, not some 22-year-old, tanned male/female roaring around in the university fitness centre. […] I also know that it means something that you feel at-home in the place you are in, and I think that I did. I am really not that fond of commercial gyms and that might be somewhere where I wouldn't feel at-home. So, in that way, it suited me very well, that it was a little worn. (FG1, standard environment)*

Participants ascribed negative attributes to the people they felt were associated with commercial gyms, for example, superficial, narcissistic, and non-professional, while participants felt the university as a setting for exercise therapy was associated with hard-working, professional, and competent

people. Both exercise environments were located at the university campus and both exercise groups made similar comparisons to commercial gym facilities.

4.3.2 Transition

Participants described markedly different experiences of entering into their respective exercise environments. Participants from the contextually enhanced environment described their entry into the room as a positive experience; the room was located in a newly built, multi-purpose university sports science facility and was in close proximity to other exercise environments in which the "professional, hard-working, and competent" people were exercising. Participants felt part of a wider exercise community, knowing there were others exercising in the building.

> *Peter:*
> *I think it was great […] to go into the changing room in the basement and up the stairs. Really, the whole starting process I thought it was good. It wouldn't be the same in a gym or in a physiotherapy clinic, really. I like it here, there is a character of a club or something. (FG1, contextually enhanced environment)*

Contrarily, participants exercising in the standard environment had to descend an enclosed staircase or use an old elevator leading to a dark basement. The basement appeared cluttered and hard to navigate, it had exposed heating pipes, stored books and unused furniture in the hallway (see Photograph 2). The entry into the room was perceived as unwelcoming and several participants reported feeling unsafe during their journey into the room.

> *Janni:*
> *But it's something with the basement, I think. The first time I came down with the elevator, it was dark. […] I'd gotten good instructions and had been taken there previously. But then I thought "what if I can't remember the way." Usually I never walk around with my mobile phone, but I took it out, because then I could always call my husband and say "I'm alone, I'm lost." (FG3, standard environment)*

These journeys or transitions into the exercise environments were pivotal when participants were forming their global impressions of their respective exercise environments for the first time. However, despite the initial negative experiences of those entering the standard environment, their perceptions changed over time, as their more positive experiences within the room imbued the space with positive meaning and value.

Mia:
But I don't think it mattered for that long.
[…]
Because then you get to know the room as the place where we do knee exercises, or as where the project takes place. (FG1, standard environment)

4.3.3 Sense of fellowship

An important difference between the environments was the reported sense of fellowship felt between participants. All participants expressed a sense of cohesion with each other—a feeling of being in the same boat—as they all had joint pain and all felt an obligation towards completing the study. The study design meant that new participants were continuously joining the exercise groups as they were enrolled. This was, however, perceived to disrupt the social dynamics of the group in both exercise environments.

Gitte:
Well, I could tell from the way the others were talking, that they knew each other a little. We were the two new ones. Even though that pasted quickly, then the others finished their exercise period, so there wasn't much sense of fellowship. Really, they were nice, but we didn't really get to know them, as we would have if we had started together. (FG3, contextually enhanced environment)

The sense of fellowship was stimulated by a number of environmental factors. Music was played in both environments during exercise sessions. In both environments, music provided a subject of conversation for participants and broke the silence. Therapists described the music as protective in the sense that the music would absorb any sighs or moans when performing the exercise and it provided privacy for having conversations with other participants without the entire group listening to the conversation. Therapists also felt that participants were more engaged in the exercise when music played.

Mikkel:
The music makes them feel safer to ask questions or to talk to other participants. Perhaps they also pushed a bit harder. If they should moan, like "Oh that was a tough repetition," they could do that if there is music, because then it is drowned out by the music. (Therapist interview)

In the contextually enhanced environment, the large window provided a view of a sport and recreational park (See Photograph 3). Some participants felt the view gave them a feeling of being part of a larger group, including those exercising outside at the purposefully designed sport and

recreational area. The view from the window provided a positive distraction for participants from the monotony of performing some of the exercises.

> *Ida:*
> *I think I liked the view, really, because it helped to distract me from the monotony or repetitiveness of the exercise.* (FG3, Contextually enhanced environment)

Although participants felt the music and the expansive view onto the sports and recreational area were positive features, they also seemed to distract participants from developing social relationships, as participants from the contextually enhanced environment stated that they did not feel part of a group and that that was something they would have liked.

> *Mette:*
> *I think it would have been better if we had been in fixed groups. […] Then you could hold each other to it; "Remember to attend the next time". It's easier to stay away when no one is holding you to it. […]*
>
> *Louise (moderator):*
> *You didn't have a feeling of being part of a group while you were here?*
>
> *Jens:*
> *No, I didn't.*
>
> *Anne:*
> *No, I didn't think so. (Extract of dialogue from FG2, contextually enhanced environment)*

In the standard environment, participants described a stronger sense of fellowship. Without the distraction from the outside view combined with the austerity of the space, participants in the standard environment seemed more conscious of each other and more at-home in the environment, leading to a strong sense of fellowship.

> *Tina*
> *From my perspective it (atmosphere) is something that motivates […] that there's a good atmosphere. And it is only there, when we feel comfortable and safe. […] It has a contagious effect. (FG3, standard environment)*
> *[…]*
> *Tina:*
> *We could talk about a lot of different things, also things that didn't have anything to do with exercise. That social, I don't know, sense of community perhaps. We were there for the same reason and we all had something to fight with, more or less. (FG3, standard environment)*

4.4 Pain relief from exercise therapy (Paper II)

To investigate that the exercise therapy performed corresponded to the effect previously reported in similar populations, an investigation of the pain relief from exercise was performed in the entire population of participants treated with exercise therapy. The two exercise groups (EX+ROOM and EX) were combined for paper II. In total, 82 participants were offered the NEMEX programme in the RCT; three participants never started the exercise therapy and one exercise diary was lost. These four participants were excluded from the analysis as no data was available.

Participants' joint pain was reduced by 1.0 NRS (95% CI 0.5 to 1.6) from 3.6 NRS at baseline (95% CI 3.2 to 4.1) to 2.6 NRS (95% CI 2.1 to 3.1) at eight-week follow-up (p<0.01) (Figure 12). A sensitivity analysis showed a clinically relevant but non-significant difference between compliant (1.3 NRS, 95% CI 0.8 to 2.0) and non-compliant participants (0.4 NRS, 95% CI -0.7 to 1.6), p=0.09.

A clear relationship was observed between time (i.e. increasing number of exercise sessions) and pain reported just before exercise sessions. The pain level on average decreased 0.04 NRS per exercise session (95%CI 0.02 to 0.05, p-value<0.01). The acute pain flare evoked by an exercise session similarly decreased over time, also by 0.04 NRS per session (95% CI: 0.03 to 0.05, p-value<0.01) (Figure 12).

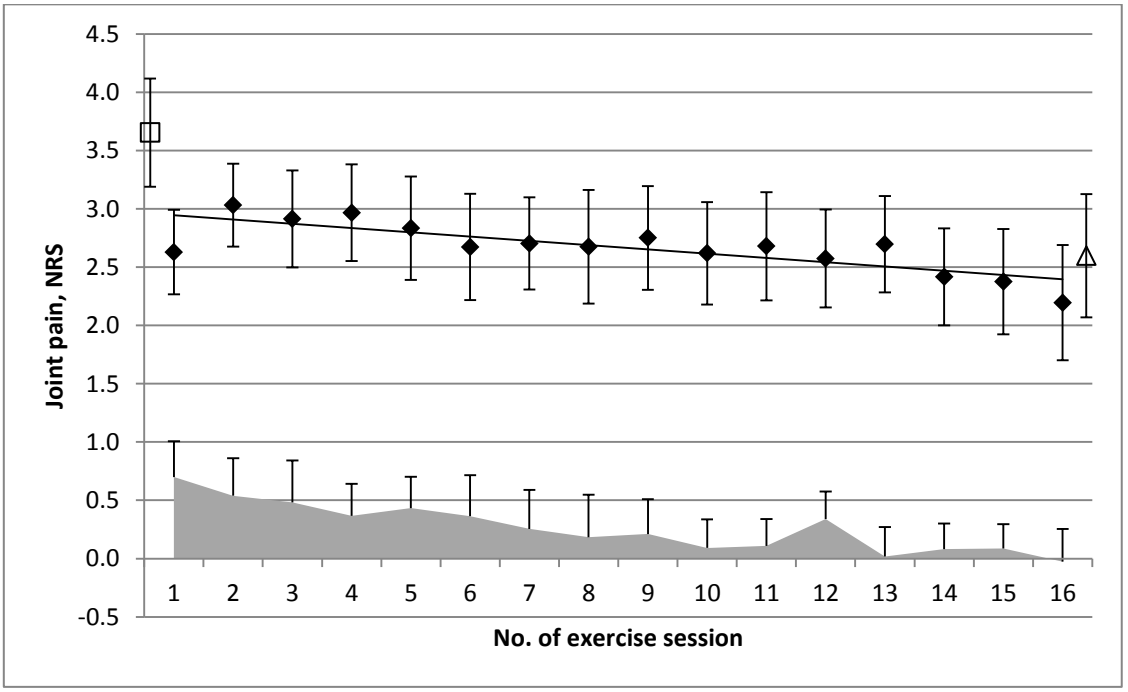


Figure 12: Pain level prior to each exercise session (black diamonds), size of acute pain flare defined as the difference from before to after each exercise session (grey area) with increasing number of exercise sessions. Pain level at baseline testing is shown by the white square and pain level at follow-up testing is shown by the white triangle. All pain ratings were given for participants' index joint on the 11-point Numerical Rating Scale (NRS). All values are group means and error-bars indicate 95 % confidence intervals. Figure from paper II.

5 DISCUSSION

5.1 Main findings

The study aim was to investigate the influence of the physical environment on treatment response to exercise therapy (Papers III). The results from the RCT study indicate that the physical environment does affect treatment outcomes in exercise therapy. Contrary to the study hypothesis, the treatment response was greater in the standard environment compared to the contextually enhanced environment. Patient-reported secondary outcomes and per-protocol analysis also favoured the standard environment over the contextually enhanced environment. The findings from the nested qualitative study provide possible explanations for the trial results. Data from the qualitative interviews suggest that participants in the standard environment experienced a strong sense of fellowship and importantly felt at-home and felt reflected and felt they fitted with the exercise environment, while those in the contextually enhanced environment seemed to lack a sense of fellowship (Paper III). As expected, participants who exercised (EX+ROOM and EX combined) reported greater improvement on a GPE scale compared to participants who received no treatment (WL). Additionally, participants who exercised had decreased joint pain after eight weeks of neuromuscular exercise therapy and a stable decrease in joint pain and size of acute exercise-induced pain flare was seen with an increasing number of exercise sessions (Paper II).

5.2 Pain relief from neuromuscular exercise therapy

The findings from paper II provide detailed information on what size of pain relief to expect from neuromuscular exercise therapy for patients with knee and hip pain. This information is important from a clinical perspective, as it may help educate patients that transient pain flares from exercise are expected, but that the pain flares will diminish with time and after six to eight weeks of exercise therapy they are no longer to be expected. Such information may motivate patients to overcome the barrier of pain-related fear associated with exercise seen in patients with OA (Heuts et al. 2004).

The pain reduction of 1 NRS point (95% CI 0.5 to 1.7) corresponded to an effect size of 0.48 (95% CI: 0.16 to 0.80); this is in line with effect sizes reported in recent meta-analyses evaluating exercise as treatment for knee and hip OA (Fransen et al. 2014, Fransen et al. 2015). Consequently, the pain reduction associated with the exercise therapy programme was considered a clinically important improvement for the study population (Salaffi et al. 2004, Perrot et al. 2013).The findings from paper II indicate that the exercise therapy programme applied in the study was effective. This combined with the finding from paper III that the treated participants reported larger improvement

in GPE than the waiting list group, indicate that the improvements seen in the exercising participants was not a result of natural disease remission or ineffective exercise therapy.

5.3 Physical environment as context factor

This is, to the author's knowledge, the first study to investigate the influence of the physical environment on the effect of exercise therapy using a randomized trial design (Paper I+ III). Factors that previously have been shown to influence health outcomes in hospital settings (see Table 1) were present in the contextually enhanced environment (see Table 3). However, this did not result in an enhanced treatment response in those exercising in the contextually enhanced environment, as hypothesised.

There are two major differences between the current study and previous studies from hospital settings which may have contributed to the discrepancy in the study results. Firstly, there was a large difference in the amount of time spent in the studied environments. In the hospital studies, once patients were admitted to the ward, they stayed in the same environment at all times during their admission. In the current study, participants spent only two hours per week within the studied exercise environments. Secondly, the administrations of treatments were different. In the hospital studies, the treatment focused on the individual patient's health problem. As a result, other patients admitted to the same ward may have had different diagnoses and received different treatments. The more serious health problems treated in hospital settings may also have affected patients in a way that they were not prone to interact socially. Consequently, a social relationship between the admitted patients may not have had the same prerequisites to develop as within this study. In this study, the exercise therapy was administered as group-based exercise twice a week for eight weeks to otherwise healthy participants. Although participants were not required to interact with each other, data from the interviews showed that social interaction occurred in both exercise environments. Interestingly, the qualitative data also suggested that the sense of fellowship was more prominent within the standard environment.

The discrepancy between results from available studies investigating the influence of the physical environment on health outcomes in hospital settings and the current study suggests that the influence of the physical environment as a context factor may differ across patient-groups, type of interventions, and health-care settings.

While the RCT showed that treatment response from exercise therapy differed when being performed in different physical environments, the qualitative study suggests that an interplay

between physical, social, and symbolic elements seemed to contribute to the trial results. This interplay may be discussed with the theoretical concept of therapeutic landscapes (Gesler 1992, Gesler 2003).

Examples of therapeutic landscapes include natural environments like hot springs or the seaside, but may also be physical environments associated with healing such as clinics, hospitals, or the general practitioner's office. However, a therapeutic landscape should not be interpreted solely as a physical landscape or the built environment, but rather as a dynamic environment entailing physical, individual, and social factors that all contribute to treatment or healing (Gesler 1992). Williams defined therapeutic landscapes as *"changing places, settings, situations, locales, and milieus that encompass both physical and psychological environments associated with treatment or healing"* (Williams 1998). Gesler describes four aspects of any therapeutic landscape: natural, built, social, and symbolic, arguing that therapeutic landscapes are best operationalised when thinking in terms of these four environments (Gesler 2003). When viewing the qualitative findings through the therapeutic landscape framework, some of these environments are recognised. A social environment is evident in the strong sense of fellowship and sense of being part of a larger exercise community. A symbolic environment is evident as participants perceived the worn environment as symbolic of their own physical state, or that the location of the exercise environment at the university was symbolic of professionalism and hard work. Consequently, aspects of the physical environment interact with both the symbolic and social environment, supporting Gesler's argument that healing and place are inseparable (Gesler 2003).

It is the experience that people have in a certain place that makes it a healing place (Williams 2002). Therefore, different physical environments may be perceived differently by different persons (Gesler 2003, Gesler 2005). As an example, Milligan and Bingley investigated the woodlands as a space for young adults to engage in recreational activity (Milligan et al. 2007). Some young adults, who had prior positive experience from woodlands from their childhood, perceived the woodlands as a restorative place. Others perceived the same woodland area as a scary space, based on prior negative experiences from their childhood, such as fairy tales or their own parents' fears (Milligan et al. 2007). For this trial, the contextually enhanced environment was hypothesised to enhance the treatment response from exercise therapy, as it entailed factors previously shown to influence health outcomes positively in other health-care settings. However, these elements were taken from one context (a hospital room) and put into a different context (an exercise environment) and may therefore have been perceived differently. From the qualitative study, it seemed that the participants' perception of a therapeutic landscape was better presented in the standard

environment than the contextually enhanced environment. Participants' prior experiences in other exercise environments, such as commercial gym facilities, sports arenas, or school gyms may have contributed participants' perception of what constitutes a therapeutic landscape for exercise therapy, and this may possibly explain why the standard exercise environment felt more like at-home than the contextually enhanced environment.

5.4 Context effects

5.4.1 The concept of context effects

As stated in the introduction, several factors other than the physical environment may contribute to the context effects of a given treatment (Di Blasi et al. 2001, Zhang et al. 2008, Doherty et al. 2009) (see Figure 1). From the model of context factors hypothesised by Di Blasi et al., all factors may act independently and potentially contribute to the treatment context (Di Blasi et al. 2001). However, factors may theoretically also interact and possibly have synergistic or mediating effects (Moerman et al. 2002, Di Blasi et al. 2003, Barrett et al. 2006, Miller et al. 2008) (Figure 13).

The current and previous studies from Kapthcuk et al. and Suarez-Almazor et al. attempt to isolate a specific factor's contribution to context effect (Kaptchuk et al. 2008, Suarez-Almazor et al. 2010). With the randomization process, all potentially contributing context factors should be equally distributed between the intervention groups resulting comparable groups at baseline and thereby isolating the intervention as the only difference between groups (Di Blasi et al. 2003). The isolated context factor in this study was the physical environment. However, the nested qualitative study indicated that a difference in sense of fellowship was evident between the two exercise environments. This suggests an interaction between context factors. Therefore, it can be discussed if it is possible to isolate a single context factor or if the sum of all potential context factors intertwined represent the context effects (Moerman et al. 2002, Miller et al. 2008, Sütterlin et al. 2015).

From this study an interaction or mediating effect seems evident between the physical environment and the social environment amongst participants and between participants and therapists. Another apparent interaction between context factors may be amongst characteristics of patients, characteristics of the practitioner and the patient-practitioner relationship (Figure 13, B). Many trials state to investigate the patient-practitioner relationship; however, when looking at the intervention performed, it is often practitioner's characteristics, like authority (White et al. 2012), or practitioner behaviour, like empathy (Kaptchuk et al. 2008, Rakel et al. 2011) and communication style (Suarez-Almazor et al. 2010) which are being manipulated to affect the patient-practitioner relationship. Similarly, patient's characteristics, such as expectation (Foster et al. 2010), previous

experiences (Conboy et al. 2010), extraversion as personality traits (Kelley et al. 2009), or female gender (Kelley et al. 2009) have been hypothesised to be supportive of the patient-practitioner relationship as well. These examples of mediating or supportive relationships underline the complexity of context effects as concept.

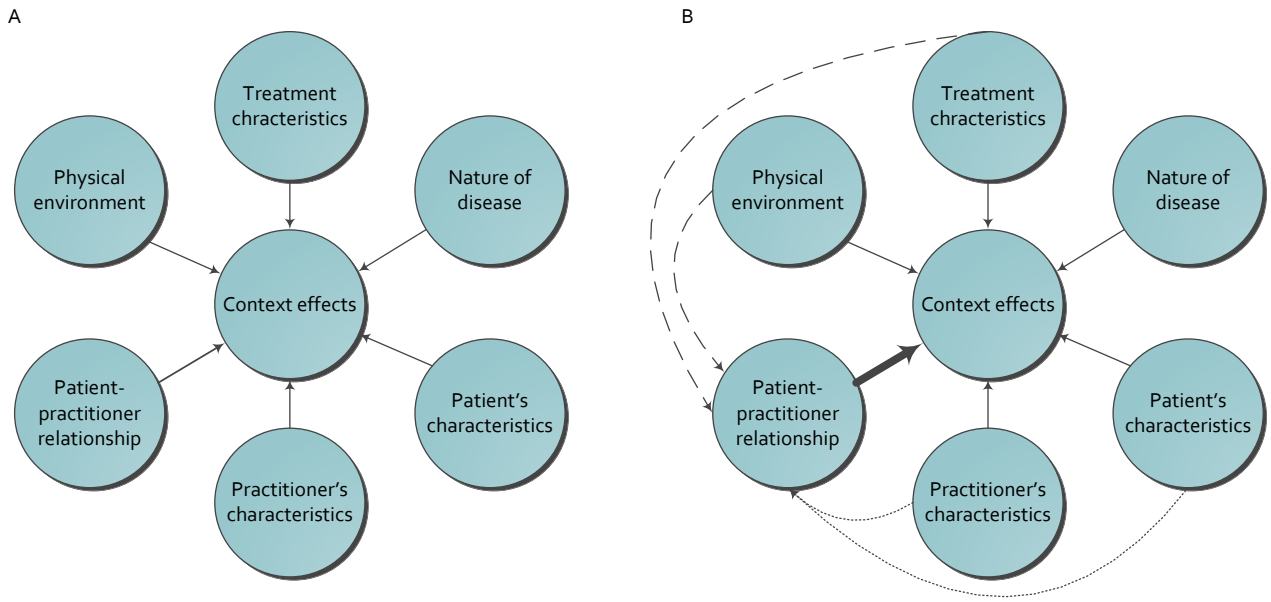


Figure 13: On the left hand side (A): All context factors contribute to context effects directly. On the right hand side (B): A more complex model of context effects is hypothesised, indicating mediating or synergistic interactions between factors contributing to context effects. The stippled lines between the physical environment and treatment characteristics to the patient-practitioner relationship indicate a possible mediating relationship as suggested by this study. The dotted lines from the patient's and practitioner's characteristics to the patient-practitioner relationship indicate a supportive relationship as suggested by literature.

5.4.2 Utilising context effects in clinical practice

There is a large clinical potential in utilising context factors to enhance treatment effect (Doherty et al. 2009, Dieppe et al. 2010, Bystad et al. 2015, Sütterlin et al. 2015). The take-home message from the current and previous studies on context effects (Kaptchuk et al. 2008, Suarez-Almazor et al. 2010, White et al. 2012) is that treatment contexts are modifiable and that context effects can be described as enhancers of existing treatment effects. Sütterlin et al. described context factors as a "toolbox of opportunities" entailing a variety of medical, clinical, psychological, environmental, and social factors that can be used to maximize treatment response individually or in combination (Di Blasi et al. 2003, Barrett et al. 2006, Doherty et al. 2009, Bystad et al. 2015, Sütterlin et al. 2015).

The advantages of utilising the physical environment as context factors is that the physical environment can be thoroughly described, and more easily and sustainably implemented or changed in existing health-care settings, whereas the patient-practitioner relationship as context factor entail elements of behaviour, communication, and personality traits which may be hard to standardise or attain across settings or in clinical practice. The plasticity of the physical environment may be exploited consciously to enhance treatment response directly or as supportive of the interplay between physical, social, and symbolic environments, as suggested by the qualitative findings. As an example, participants in this trial perceived commercial gym facilities as inappropriate and emphasised the social relationship with other participants. Choosing an older, more familiar building for exercise therapy may support the social environment and feeling of being at-home in the exercise environment which could create a more optimal treatment context for the given population. Contrarily, if the exercise therapy in this study had concerned younger elite athletes with sports injuries, who have positive experiences with commercial gym facilities, their perception of physical environments might be quite different. Consequently, giving greater attention to matching the physical environment for exercise therapy to the attitudes and preferences of the users in clinical practice may be used to enhance self-reported health.

5.4.3 Ethical considerations

As for the definitions of placebo and context effects, the ethical considerations associated with the two concepts differ as well. For studies of placebo effect, administering inert treatments constitutes an ethical concern (Kaptchuk 1998). When given inert treatment, patients may be held in their disease state for a prolonged period of time or may experience harmful side effects, when they could have been given active treatments. However, it is important to recognise that placebo-controlled studies are invaluable and necessary to assess effectiveness and safety of new treatments (Beecher 1955, Di Blasi et al. 2003). The use of placebo in medical research may therefore be justified. However, the use of placebo outside trials and research settings have been argued as uncontrollable and unethical (Hróbjartsson 1996, Hróbjartsson 2008).

Contrary to placebo-controlled studies, both intervention groups are given similar treatment in studies of context effects. Additionally, one intervention group is treated in an enhanced treatment context that hypothetically may enhance treatment effect (Figure 14) (Kaptchuk et al. 2008, Suarez-Almazor et al. 2010). One might argue that studies of context effects, just like studies on placebo effect, similarly entail an ethical dilemma as the potentially enhancing effect is withheld from the standard intervention group. However, the standard intervention group is given treatment just as

they would be in clinical practice, and—although a greater treatment effect is hypothesised in the contextually enhanced context—it is not confirmed until the trial is completed. The identification of both effective treatments and optimal treatment contexts are in the patients' best interest (Doherty et al. 2009, Finniss et al. 2010), which speaks for studies on placebo and context effects.

5.5 Methodological considerations

5.5.1 Randomised controlled trial design

The three-armed RCT design used in this study has several advantages. In research on placebo effect it has been discussed whether the observed placebo effect can be explained merely by natural disease remission or regression towards the mean (Thompson 2000, Hróbjartsson et al. 2001, Hróbjartsson et al. 2003, Hróbjartsson et al. 2004, Krogsboll et al. 2009). To eliminate both these terms as explanation for the study results, the waiting list group was included as an untreated reference group (Di Blasi et al. 2003, Kaptchuk et al. 2008). As the waiting list group did not receive treatment, it represents the natural disease progression for the study population (Kleijnen et al. 1994). Then, by comparing the treated participants (EX+ROOM and EX groups combined) to the untreated participants (the waiting-list group), the possibility that the reported treatment effect may be caused by natural disease remission is eliminated (see Figure 14, A). In this study, the participants who exercised (EX+ROOM and EX groups combined) showed significant improvement compared to the waiting list (WL vs. EX+ROOM and EX combined, p=0.05). The context effects attributed to the isolate context factor may then be investigated by comparing the standard intervention group and the enhanced intervention group (Figure 14, B).

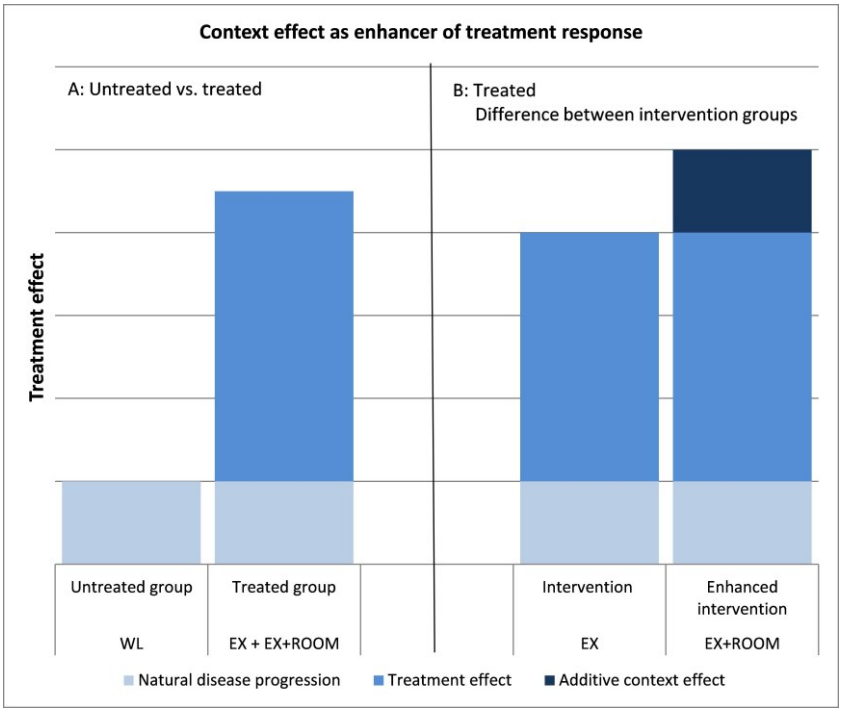


Figure 14: Schematic overview of the three-armed study design. The light blue colour represents the natural disease progression present in all groups, quantified by the untreated control group. The blue colour represents the treatment effect attributed to the specific treatment. When investigating whether the treatment effect observed is attributable to natural disease remission, the untreated participants and treated participants (both treatment groups combined) are compared (part A). When investigating an additive contextual effect of the enhanced intervention, the intervention group and enhanced intervention group are compared (part B). The dark blue colour represents the additive treatment effect originating from the enhanced treatment context.

The randomisation of participants was an imperative element of the study design, as it was fundamental in order to isolate the physical environment as the only difference between groups. As a result of the randomisation, the participants' characteristics should be equally distributed between groups (Di Blasi et al. 2003, Bishop et al. 2015). Several actions were additionally taken to isolate the physical environment as the only difference between groups in this trial. The exercise therapy programme was standardised and the supervision of the exercise therapy was standardised by certifying the supervising therapists and having the same therapists supervise in both exercise environment (Bishop et al. 2015). Consequently, both the treatment characteristics (exercise therapy programme) and the practitioner characteristics (supervising therapists), and the patient-practitioner relationship should be similar across the exercise environments. However, as discussed previously, the data from the nested qualitative interview questions whether the isolation of a specific context factor is possible, as discussed previously.

The three-armed RCT design also allows for a test for trend across intervention groups. This analysis was previously applied in the Kaptchuk study that found a positive trend across the intervention groups in the order, waiting list < limited relation < augmented relation (Kaptchuk et al.

2008). The authors concluded that a dose-response-like relationship between quality of the patient-practitioner relationship and treatment response was evident (Kaptchuk et al. 2008). In the current study, the same test for trend was performed, in the a-priori hypothesised order: waiting list < exercise in standard environment < exercise in contextually enhanced environment. However, as the primary outcome favoured the standard environment over the contextually enhanced environment, the test for a trend in the hypothesised order was insignificant (p=0.36).

5.5.2 Combining quantitative and qualitative research methods

One of the major strengths of this study is the combination of quantitative and qualitative methods, as it provided a more nuanced and complete understanding of the influence of the physical environment on the effect of exercise therapy (Malterud 2001, Di Blasi et al. 2003, O'Cathain et al. 2013). Without doubt, the qualitative data provided possible explanations to the study result, shed light on the complexity of context effects as a concept, and informed on recommendations regarding the physical environment in clinical practice. In qualitative research, the researcher is an active part in the development of knowledge and may explore thoughts, social relations, and interactions between study participants (Malterud 2001). The strength of the qualitative research is that it can explore the width of a research question by investigating consistencies and discrepancies in the data, whereas, the strength of the quantitative method lies in its ability to answer a specific research question using statistical tests, providing generalizability and certainty in the results (Malterud 2001).

The nested qualitative study entailed focus group interviews with participants. An advantage of focus groups is that participants may reflect upon the conversation with other participants during the interview (Finch et al. 2014). Participants may also ask each other questions that may bring forth aspects unknown to the researcher. However, it is important to recognise that especially the group dynamics may influence the quality of the interview. Some participants may be more dominant than others and some participants may be reluctant to share thoughts with others, whom they do not know well (Finch et al. 2014).

An advantage of the photo-elicitation technique applied is that the photographs may evoke both verbal and non-verbal reactions in participants and provide deeper, more elaborate responses (Harper 2002). Several participants had non-verbal reactions when recalling the smell, temperature, or feelings from the exercise environments. The photo-elicitation technique also provided a natural transition from the general questions about the exercise therapy in to a more narrow focus on the physical environment. Consequently, a deliberate unblinding of the participants was avoided, which potentially may have jeopardized participants' trust in the study.

6 CONCLUSIONS

- The trial results indicate that the physical environment does influence treatment effect from exercise therapy. Contrary to the trial hypothesis, the treatment response was greater in the standard exercise environment compared to the contextually enhanced environment (Paper III).

- The nested qualitative study suggested that giving greater attention to matching the physical environment for exercise therapy to the attitudes and preferences of the intended users may enhance patient-reported treatment effects from interventions such as exercise therapy (Paper III).

- A clear decrease in size of acute exercise-induced pain flares and overall joint pain was seen with increasing number of exercise sessions in an 8-week neuromuscular exercise therapy programme (Paper II).

7 RECOMMENDATIONS FOR EXERCISE ENVIRONMENTS IN CLINICAL PRACTICE

This thesis provides valuable information about how the physical environment of exercise therapy is perceived by patients. The following recommendations for the physical environment of exercise therapy in clinical practice are based on qualitative interviews with participants and therapists.

Mirrors are used as tools in exercise therapy to provide visual feedback. However, participants expressed insecurity and discomfort with the mirrors.

1) Explain the purpose of the mirrors and motives for their use.
2) Restrict mirrors to one wall, for several reasons:
    a. Participants dislike seeing their reflection from more than one angle
    b. Participants are concerned they might be observed in the mirrors by others
    c. The number of people may be perceived as doubled if there are mirrors on opposite walls.

Music during exercise was perceived as a positive distraction and aided the social interaction.

1) Music should be played at a level allowing conversation and verbal supervision
2) Music should not be loud or throbbing
3) Music should be age-group appropriate and preferably remind participants of their youth.

Way finding may be perceived as a barrier, especially when attending exercise for the first time.

1) Give directions to the exercise and changing rooms, preferable by walking together with patients
2) Way finding may be aided by “way markers” on stairs, arrows on the floor and signs on doors

Feeling part of a group and feeling at-home contributed to making the exercise environment a therapeutic place for participants. Factors that contributed to this feeling included:

1) The exercise environment being enclosed
2) The exercise environment allowing participants to create routines. Examples of routines may be: doing specific exercises on specific places, helping set out equipment, having set routines for starting and ending the exercise session
3) Considering having fixed groups starting and ending the exercise therapy together
4) Calling participants by their first name and introducing new participants.

8 SUMMARY

Context effects are defined as the effects of a given treatment, not directly caused by the treatment itself, but, rather, caused by the context in which the treatment is delivered. The patient-practitioner relationship is a known context factor, but it is hard to standardize across health-care settings. The physical environment is easier to standardize and may act as a context factor and influence treatment outcomes. Studies from hospital environments have shown that the physical environment influences health outcomes, patients, and clinicians. It is unknown if the physical environment affects treatment outcomes in other health-care settings, such as rehabilitation and exercise therapy settings. The aim of this thesis was to investigate the role of the physical environment as a contributor to context effects in the treatment response from exercise therapy as treatment for muskuloskeletal pain.

In a randomised controlled double-blind trial (RCT), 103 participants were randomised in a 2:2:1 allocation to three groups: 1) 42 participants exercised in a contextually enhanced environment, 2) 40 participants exercised in a standard environment, and 3) 21 participants were on a passive waiting list. Middle-aged individuals reporting persistent knee or hip pain within the past three months were eligible to participate. Eight weeks of group-based neuromuscular exercise therapy, supervised by the same therapists, was performed in either a newly built contextually enhanced environment or in a standard old, unenhanced environment. The passive waiting list group received no exercise therapy prior to the eight-week follow-up. Both participants and the supervising therapists were blind to the study aim. Participants self-reported joint pain on an 11-point numerical rating scale (NRS) before and after each exercise session. The primary endpoint was participants' global perceived effect (GPE) assessed on a 7-point Likert scale at the eight-week follow-up. A qualitative study was nested into the RCT including six semi-structured focus-group interviews with participants (n=25) and individual interviews with therapists (n=2) exploring experiences and perceptions of the physical environments.

The waiting-list group reported no significant improvement (-0.05 GPE, CI 95% -0.5 to 0.4). Contrary to the study hypothesis, participants exercising in the standard environment reported greater improvement in GPE (0.98, CI 95% 0.5 to 1.4) than participants exercising in the contextually enhanced environment (0.37, CI 95% -0.2 to 0.9), p=0.07.Patient-reported secondary outcomes and qualitative findings similarly favoured exercise in the standard environment over exercise in the contextually enhanced environment. In interviews, participants from the standard environment stated that they felt at-home, experienced a strong sense of fellowship, and identified their own body image with the standard environment. The mean age of the study population was 58.5 years,

63% had knee pain as primary complaint, 61% were women and 88% reported joint pain for more than one year. As expected, participants attending neuromuscular exercise therapy reduced their joint pain over time with 0.04 NRS (95% CI 0.02 to 0.05, p<0.01) per exercise session. Similarly, the size of their acute exercise-induced pain flare decreased 0.04 NRS (95% CI 0.03 to 0.05, p<0.01) per exercise session.

The results of this study indicate that the physical environment does influence treatment effects from exercise therapy, suggesting that the physical environment contributes to context effects. Matching the physical environment in exercise therapy to the preferences of the intended users may enhance self-reported treatment effects. Furthermore, the study results support previous research that neuromuscular exercise therapy provides pain relief for individuals with persistent knee or hip pain.

9 DANSK RESÚME

Kontekseffekt defineres som effekten af en given behandling, som ikke skyldes selve behandlingen, men i højere grad den kontekst som behandlingen foregår i. Forholdet imellem patient og behandler vides at bidrage til kontekseffekt, men kan være svært at standardisere. Det fysiske miljø er lettere, at ensrette og kan muligvis bidrage til kontekseffekt. Studier har vist, at det fysiske hospitalsmiljø kan påvirke både patient, personale og behandlingseffekt. Formålet med denne afhandling var at undersøge påvirkningen fra det fysiske miljø på effekten af træning som behandling af muskuloskeletale smerter.

I et randomiseret kontrolleret dobbelt-blindet studie (RCT) blev i alt 103 deltagere randomiseret til 3 grupper: 1) 42 deltagere trænede i et kontekstforbedret træningsmiljø, 2) 40 deltagere trænede i et standard træningsmiljø og 3) 21 deltagere var på passiv venteliste. Midaldrende personer med knæ- eller hoftesmerter vedvarende i mere end 3 måneder kunne inkluderes i studiet. Otte ugers gruppebaseret neuromuskulær træning, superviseret af de samme fysioterapeuter, blev gennemført i enten et kontekstforbedrede træningsmiljø, som fremstod nyt og moderne, eller i et standard træningsmiljø, som fremstod gammelt og brugt. Deltagerne, og de superviserende fysioterapeuter, var blindede for studiets formål. Deltagerne selv-rapporterede ledsmerter på en 11-punkts numerisk rangskala (NRS) før og efter hver træningssession. Det primære effektmål var deltagernes opfattelse af den overordnede behandlingseffekt (GPE) vurderet på en 7-punkts Likert skala ved studiets afslutning. Et kvalitativt studie var indlejret i RCT studiet bestående af 6 semistrukturerede fokus-gruppe interviews med deltagere (n=25) og individuelle interview med terapeuter (n=2). Formålet med interviewene var, at undersøge deltagernes og terapeuternes oplevelser og erfaringer fra de to træningsmiljøer.

Som forventet rapporterede deltagere på venteliste ikke nogen forbedring (-0,05 GPE, KI 95% -0,5 til 0,4) ved studiets afslutning. Deltagere som trænede i standard træningsmiljøet rapporterede større forbedringer i GPE (0,98, KI 95% 0,5 til 1,4) sammenlignet med deltagere som trænede i det kontekstforbedrede træningsmiljø (0,37, KI 95% -0,2 til 0,9), p=0,07. Selv-rapporterede sekundære effektmål og de kvalitative interviews favoriserede tilsvarende standard træningsmiljøet over det kontekstforbedrede træningsmiljø. I interviewene gav deltagere fra standard træningsmiljøet udtryk for en stærk fællesskabsfølelse, samt at de følte sig hjemme og tilpas i træningsmiljøet. Studiets deltagere havde en gennemsnitsalder på 58,5 år, 63% havde primært knæsmerter, 61% var kvinder og 88% havde haft smerter i mere end 1 år. Som forventet reducerede deltagere randomiseret til den neuromuskulære træning deres ledsmerter med 0,04 NRS (95% KI 0,02 til 0,05, p< 0,01) pr.

træningssession. Tilsvarende reduceredes størrelsen af det akutte træningsinducerede smerterespons med 0,04 NRS (95% KI 0,03 til 0,05, p=0,01) pr. træningssession.

Resultaterne fra denne afhandling indikerer, at det fysiske miljø påvirker effekten af træning som behandling for knæ- eller hoftesmerter, og antyder at det fysiske miljø bidrager til kontekseffekt. Større opmærksomhed på at tilpasse det fysiske miljø til brugerenes præferencer kan muligvis forstærke selvrapportret behandlingseffekt. Yderligere finder afhandlingens resultater som tidligere forskning, at deltagelse i neuromuskulær træning har smertelindrende effekt hos personer med vedvarende knæ- eller hoftesmerter.

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APPENDICES

Paper I

BMJ Open

Exploring the effect of space and place on response to exercise therapy for knee and hip pain—a protocol for a double-blind randomised controlled clinical trial: the CONEX trial

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ABSTRACT

Introduction: *Context effects* are described as effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context in which treatment is delivered. Exercise is a recommended core treatment in clinical guidelines for musculoskeletal disorders. Although moderately effective overall, variation is seen in size of response to exercise across randomised controlled trial (RCT) studies. Part of this variation may be related to the fact that exercise interventions are performed in different physical environments, which may affect participants differently. The study aims to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks in people with knee or hip pain.

Methods and analysis: The study is a double-blind RCT. Eligible participants are 35 years or older with persisting knee and/or hip pain for 3 months. Participants are randomised to one of three groups: (1) exercise in a contextually enhanced environment, (2) exercise in a standard environment and (3) waiting list. The contextually enhanced environment is located in a newly built facility, has large windows providing abundant daylight and overlooks a recreational park. The standard environment is in a basement, has artificial lighting and is marked by years of use; that is, resembling many clinical environments. The primary outcome is the participant's global perceived effect rated on a seven-point Likert scale after 8 weeks exercise. Patient-reported and objective secondary outcomes are included.

Ethics and dissemination: The Regional Scientific Ethical Committee for Southern Denmark has approved the study. Study findings will be disseminated in peer-reviewed publications and presented at national and international conferences.

Trial registration number: NCT02043613.

Strengths and limitations of this study

- The randomised controlled trial aims to investigate the effect of the physical environment on the effect of exercise therapy.
- The study focuses on the significance of the context in which treatment is delivered.
- The physical environment is a single component of the multifactorial concept of contextual effect, and isolating only one component may be difficult as interaction between several components may occur.

INTRODUCTION

The physical environment affects the persons in it and may potentially be of significance for health and treatment effects. Studies on the role of physical environments conducted in hospital settings have reported that factors such as noise, daylight deprivation and light intensity may increase stress and pain level, reduce patient satisfaction and affect length of hospital stay.[1–5] Many rehabilitation and hospital exercise facilities are today located in large rooms in basements or other windowless rooms with poor acoustics, not designed for optimal exercise therapy delivery. Such inexpedient physical environments may affect patients negatively and potentially result in a poorer result from the exercise or rehabilitation, if patients are feeling unwelcomed or are not motivated to comply with the exercise in the given environment. Theoretically, enhanced physical environments may create a positive atmosphere, enhance communication during exercise and potentially improve exercise performance, compliance and perceived well-being. Exercise is recommended as a lifelong treatment for chronic diseases such as cardiovascular diseases, diabetes and musculoskeletal disorders, including hip and knee osteoarthritis (OA) and joint pain. Despite the high-level evidence that exercise provides on

average moderate pain relief and functional improvement in patients with OA, large variation in effect is observed across studies and treatment effects may vary from small to large.[6 7] In addition to differences in characteristics of the exercise programmes studied, this may also relate to the fact that exercise interventions have been performed in different physical environments and that these environments may influence patients differently.[8] It is plausible, but currently unknown, whether the physical environment can be modified in ways that enhance the effect of exercise therapy. To the best of our knowledge, this is the first trial to actively investigate if modification of the physical environment can be used in a positive way to enhance the effect from exercise therapy.

This study applies the term 'context effect' as a framework for elucidating how treatment effect is potentially caused by a complexity of factors in addition to the actual treatment effect. Context effects are defined as the effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context or environment in which the treatment is given.[8–11] Context effects may be considered as a parallel to placebo effects, which have been one of the most debated topics in modern medicine.[12–15] Several authors have objected to the term placebo, as they argue that the definition is self-contradictory and inadequate.[9 16–19] Placebo is classically defined as giving an inert substance or treatment.[10 18] However, if placebos are inert, they cannot have an effect, and if they have an effect, they cannot be inert.[9 10 16 18] Other terms have been suggested, such as non-specific effect, non-characteristic effect, incidental effects, meaning response, placebo components and context effects, as applied in this study.[9 20–24] A clear distinction should be made between placebo effects and context effects. Placebo is associated with giving pills, injections or having surgery and often entails a form of deliberate deception, whereas context effects rather classify factors creating or enhancing a treatment effect.[8–11] Factors contributing to context effects can be divided into different categories, such as characteristics of the patient and the practitioner, type of treatment, nature of disease and the physical environment.[8 11] This study will focus on the physical environment where exercise therapy is delivered, as it can be modified in a standardised and reproducible way to potentially enhance adherence and enhance the positive effects of exercise therapy.

The study aim is to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks in people with knee or hip pain. We hypothesise that participants exercising according to a standardised programme in a contextually enhanced physical environment will report greater improvement from exercise compared with participants following the same exercising programme in a standard physical environment as measured by patients' global perceived effect (GPE). Further, we expect that the two exercise groups will be superior to a passive waiting list (WL).

METHODS AND ANALYSIS

Study design

This study is designed as a three-armed randomised controlled clinical trial. Participants are randomised to three intervention groups: exercise in a context enhanced physical environment (EX+ROOM), exercise in a standard physical environment (EX) or WL. Participants, investigators and exercise instructors are blinded to treatment allocation. The primary end point is the patient's GPE assessed after 8 weeks exercise on a seven-point Likert scale. Results from this study will be reported according to the CONSORT statement.[25]

Participants

Eligible participants are 35 years or older, self-reporting persisting knee and/or hip pain within the past 3 months and are willing and able to attend exercise therapy twice weekly at the University of Southern Denmark, Odense M. Exclusion criteria are: (1) comorbidities or contraindications prohibiting participation in exercise therapy; (2) inability to answer questionnaires or to speak, read or understand Danish; (3) already participating in exercise therapy, defined as an exercise programme supervised by a physiotherapist, or systematic training with a duration of 6 weeks or more started within 3 months to inclusion, aimed specifically at relieving knee or hip joint problems; (4) having had surgery to the hip/knee within the past 3 months or waiting for joint surgery in the coming 6 months. Participants are recruited via different pathways: posters and informational leaflets at general practitioners' offices, the orthopaedic department at Odense University Hospital or participant initiated contact through posters and articles in local newspapers, social media and word of mouth (figure 1). Participants are screened via telephone and, if eligible, they are invited to a baseline visit and written information is sent to the participants. At the baseline visit, the primary investigator gives oral information regarding the study and the participant signs the consent form if they are willing to participate. Baseline testing is performed directly hereafter.

Intervention

Participants are randomly assigned to one of three groups.

Group EX+ROOM: exercise in a contextually enhanced physical environment

This exercise room is placed on the second floor in a newly built facility. It has a view to a newly reconstructed outdoor sport and recreational park. It has not been previously used in studies investigating exercise as a treatment option.

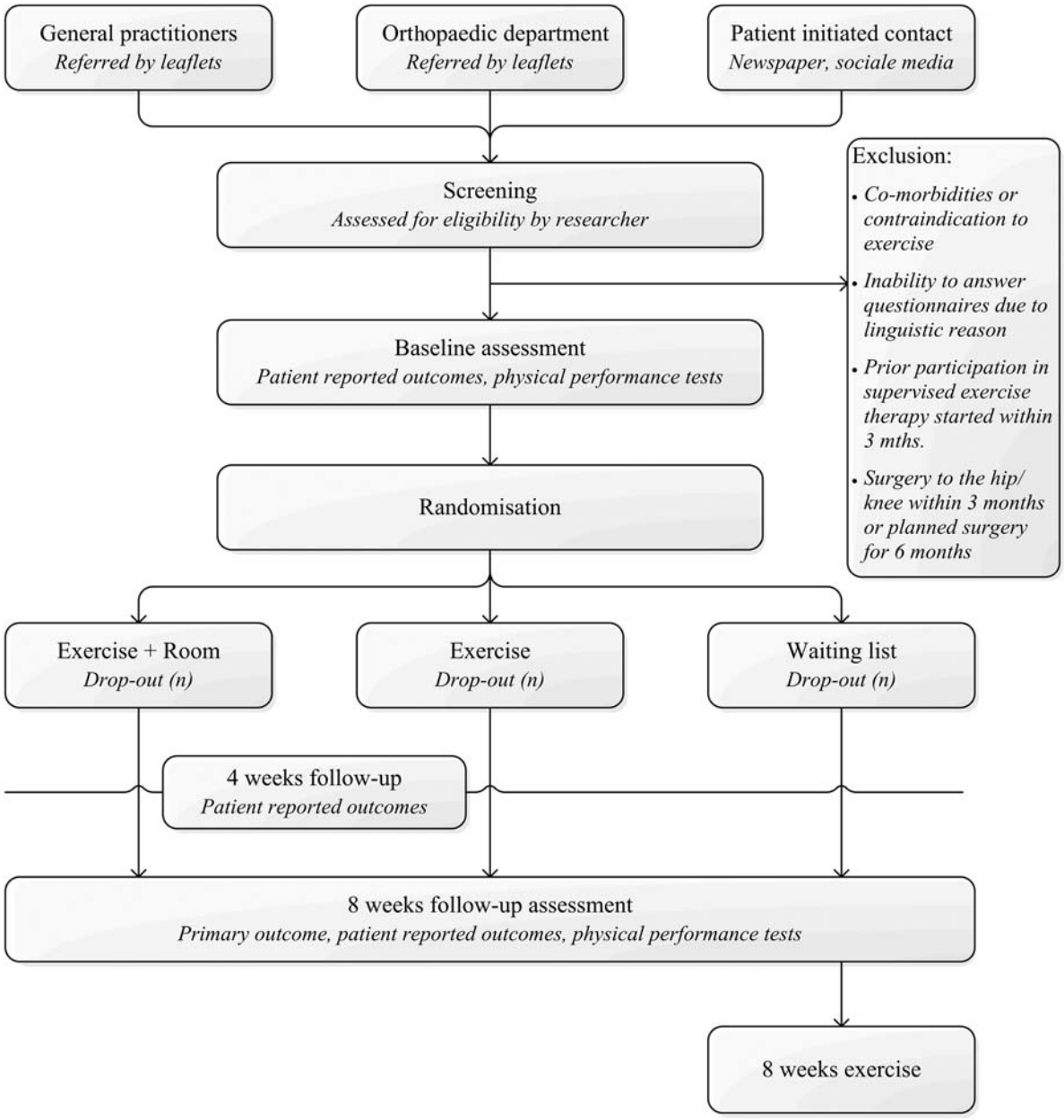

Figure 1 Flow chart, overview of the recruitment flow in the CONEX trial.

Group EX: exercise in a standard physical environment

This group will exercise in a room, which has been used in other exercise studies. The room is marked by years of use. It is placed in the basement and accessed through a series of staircases and hallways through the basement. This facility resembles many existing exercise facilities at hospitals and rehabilitation clinics and is considered a standard exercise environment.

Contextual factors

The physical environments are described and classified by a variety of contextual factors (table 1).

Acoustic properties such as speech interpretability, reverberation and background noise are measured by use of standard acoustic methods.[26] Better acoustic properties, such as shorter reverberation time and higher speech interpretability, may reduce stress and improve communication. In hospital environments, high noise levels are associated with worse patient outcomes such as psychological stress and satisfaction with care.[27] Background noise (dB(A)) is measured in empty rooms. Reverberation is measured as T20, the time interval for a 20 dB decay within a room. Reverberation is a measure of how long it takes for sound to decay in a room and a long reverberation time affects speech comprehension negatively.[26] Reverberation and speech interpretability are descriptive of how well speech is perceived in a room. Speech interpretability is measured as speech clarity and transmission. Speech clarity is measured as Clarity Index within the initial 50 ms (C50); it compares

Table 1 Descriptive environmental factors

Dimension	Factor	Contextually enhanced physical environment	Standard physical environment
Indoor environment	Light		
	Strength (Lux)	@	@
	Source	Daylight + artificial light	Artificial light
	Window/no window	Windows, floor to ceiling	No windows
	Air quality		
	CO_2 (ppm)	@	@
	Temperature (°C)	@	@
	Humidity (%)	@	@
	Sound/noise		
	Background noise (dB(A))	@	@
	Speech clarity (C50, STI)	@	@
	Reverberation (T20)	@	@
Décor	Wall decorations	Picture of nature scenes	No decorations
	View	View of nature and outdoor exercise environment	No view

Parameters assessed in the different physical environments @=assessed/measured and will be reported.
C50, clarity index with first 50 ms of sound; ppm, parts per million; STI, Speech Transmission Index; T20, reverberation time for sound decay of 20 dB.

early sound reflection with later sound reflection. Early sound reflections are positive for speech interpretability and later sound reflection will be perceived as noise. A high C50 indicates good speech interpretability. Speech Transmission Index (STI) is a measure of sound quality in transmission from sound source to receiver. Reverberation and speech interpretability are derived from tape recordings of loud clear noises emitted in the exercise rooms. Acoustic measures are obtained from two positions in the room with small, medium and large distance to the sound source. Light intensity is assessed using an adapted method from Walch *et al*.[29] Light intensity is measured using a LUX meter (Amprobe, LM-100, light meter, Everett, Washington, USA) in two representative positions in the exercise rooms and additionally directly at windows, if present in the room. Three consecutive measures are obtained from each position and averaged. Light measurements are taken as close to the exercise time as possible. Daylight and brighter rooms are associated with lower pain perception and lower postoperative analgesic intake in hospital environments.[28 29] Air quality is described by CO_2 concentration, temperature and air humidity in the exercise rooms during exercise. It is assessed with an air quality data logger, set to collect data at 30 s intervals (Trotec, BZ-30, data logger, Heinsberg, Germany). Furthermore, carefully selected pictures of nature scenes are hung in a contextually enhanced physical environment. Viewing nature pictures or visual stimuli of nature elements has been known to reduce stress in an office setting and influence recovery time and decrease pain in patients following surgery.[1 5 30–33]

Exercise

The exercise programme for participants in the EX+ROOM and EX group is based on the standardised NEuroMuscular EXercise (NEMEX) programme. It is described in detail elsewhere[34] and has previously been investigated for feasibility in patients with severe knee or hip OA.[34] The NEMEX programme is based on biomechanical and neuromuscular principles, which aim to improve sensorimotor control and achieve functional stability.[34] The NEMEX programme has previously been shown to be effective in relieving pain and improving function in populations with knee or hip pain such as anterior cruciate ligament injuries,[35–38] meniscectomised participants,[39 40] and patients with hip or knee OA undergoing total joint arthroplasty.[34 41] Exercise is performed as a group exercise, and all exercise sessions are supervised. All instructors will be certified in the NEMEX programme. To ensure consistency between instructors, they will participate in a 2-day course, Good Life with OA in Denmark, focusing on lower limb OA management and neuromuscular exercise. After completing the course, all instructors will go through the exercise programme with the primary investigator to ensure consistency in instructing and supervising exercise as well as going through how volume, load and progression of exercise and pre-exercise and postexercise pain should be documented in participants' exercise dairies. The EX+ROOM and EX group will exercise on the same weekdays, twice a week for 1 hour duration. An instructor will first supervise the EX+ROOM group and then the EX group. Consequently, all of the instructors will have supervised the NEMEX programme in both physical environments and for the same amount of time, that is, if an instructor supervises the EX+ROOM group, then they will supervise the EX group as well. This is done to ensure consistency in delivery instructions and supervision of exercise across study participants and to ensure that any

effect that a given instructor may have on the exercise and participants should be similar between physical environments.

Group WL: WL/control group

Participants randomised to a WL are placed on a passive WL for a period of 8 weeks, and thereafter offered 8 weeks of structured resistance exercise. These participants act as an observational group and represent the natural course of disease in participants with knee and/or hip pain. After the 8 weeks when follow-up data for the current study have been collected, the participants are offered resistance exercise rather than neuromuscular exercise for logistic reasons, such as avoiding taking up place in the designated exercise rooms used in the study and consequently affecting the time to completion of the study.

Primary outcome

Participants' GPE assessed at 8 weeks will be the primary end point of the trial. Participants are asked to respond to the following question: *Compared to before you entered the study, how are your knee/hip problems now?* on a seven-point Likert scale. The GPE scale ranges from 'markedly worse' through 'no change' to 'markedly improved'. GPE is a reliable method for measuring the effect of clinical interventions.[42 43] It has previously been used in studies investigating contextual effect of treatment.[44] The validity of GPE scales has been questioned. However, a study on the correlation between transition ratings and prescore and postscore of quality of life questionnaires showed a correlation of 0.8 between the change score of the questionnaire and the transition ratings suggesting that transition scales, such as GPEs, are valid for detecting changes and can be used in clinical trials as primary outcome measures.[43]

Secondary outcomes

All outcomes and time points for data collection are listed in table 2.

Patient-reported outcomes

Participants answer the Danish versions of the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip disability and Osteoarthritis Outcome Score (HOOS) depending on either knee or hip problem

Table 2 Summary of collected data and time points

Variable	Baseline	4 weeks	8 weeks
Baseline data			
Height (cm)	@	NA	@
Weight (kg)	@	NA	@
Age (years)	@	NA	NA
Gender (F/M)	@	NA	NA
Marital status	@	NA	NA
Educational level	@	NA	NA
Employment status	@	NA	NA
Alcohol consumption	@	NA	NA
Smoking	@	NA	NA
Physical activity level at work and leisure	@	NA	NA
Primary outcome			
Global perceived effect (7-point Likert scale)	NA	@	@
Secondary outcomes			
Patient-reported outcomes			
Knee/Hip Injury and Osteoarthritis Outcome Score	@	@	@
Short-form 36 Health Survey	@	@	@
Modified Arthritis Self-Efficacy Scale	@	@	@
Patient Acceptable Symptom State (y/n)	NA	NA	@
Patient satisfaction (5-point Likert scales)	NA	NA	@
Stress (100 mm VAS)	@	NA	@
Objective physical function tests			
Aerobic capacity (ml O_2/min/kg)	@	NA	@
Isometric strength hip abduction (Nm)	@	NA	@
Isometric strength knee extension (Nm)	@	NA	@
Single-limb mini squat	@	NA	@
Knee bends/30 s (n)	@	NA	@
Chair stands/30 s (n)	@	NA	@
Walking test, 40 m fast paced (s)	@	NA	@
One leg hop of distance (cm)	@	NA	@

Summary of primary and secondary outcomes and respective time collection points.
@, assessed/measured; F, female; M, male; NA, not assessed; VAS, visual analogue scale.

being the primary cause of pain. The KOOS and HOOS are joint-specific questionnaires, developed to assess participants' opinion about their knee or hip problems.[45 46] They consist of five subscales: pain, symptoms, activities of daily life function, sport and recreational function, and joint-related quality of life.[47] Each subscale consists of a set of items specific to the subscale and each item is assessed via a Likert scale with five possible answer options ranging from 0 (no problems) to 4 (extreme problems). The Likert score is transformed into a 0–100 scale with 0 representing extreme knee problems and 100 representing no knee problems.[45] The KOOS and HOOS have good psychometric properties for patient groups with knee injury, knee replacement, hip dysfunction and hip replacement.[46–50]

The Medical Outcome Study 36-item short form general health survey (SF-36) is a generic patient-reported health status measure.[51–53] It consists of 36 items organised under eight subscales: (1) physical functioning, (2) role limitations because of physical health, (3) bodily pain, (4) social functioning, (5) general mental health, (6) role limitations because of emotional problems, (7) vitality and (8) general health perception.[53] Low scores indicate limitations in activities and a perception of poor health, while high scores indicate no limitations and good health.[53] Validity and reliability of the SF-36 is adequate and the questionnaire is widely used.[51 52]

A modified measure of self-efficacy is included to evaluate patients' perception of functionality or limitations to their functionality caused by their knee or hip problem. Self-efficacy is defined by Bandura[54] as "belief in one's capability to organise and execute the course of action required to produce given attainments". Self-efficacy is assessed with a modified version of the Arthritis Self-Efficacy Scale (ASES)[55] previously used in a similar patient group.[56] The modified version of ASES consists of 11 single items from the two subscales, pain and other symptoms. Participants rate their ability to cope with pain and symptoms related to their joint problem on a 10–100 scale, with 10 indicating very uncertain and 100 indicating very certain with 10-point increments.[57]

A series of single-item questions are included. The Patient Acceptable Symptom State is assessed by asking a single yes/no question: "Considering your knee function, do you feel that your current state as satisfactory? With knee function you should take into account all the activities you have during your daily life, your level of pain and other symptoms and your quality of life."[58] If participants rate their current symptom state as unacceptable, a follow-up question is asked as to whether they consider the treatment to have failed. Further, participants are asked to answer five GPE questions specific for each of the five subscales of either the KOOS or HOOS, rating either improvement or deterioration and finally an indication of whether these changes are perceived as important or unimportant by the participants. These single items are included in order to assess minimal clinical important changes for the five subscales of the KOOS and HOOS. Stress is estimated as 'general stress level' measured on a 100 mm visual analogue scale ranging from no stress to stress as severe as could be.[59]

Patient-reported outcomes are collected using an online survey. At baseline and 8 weeks follow-up, participants answer the survey on a computer in the examination room without the investigator being present. At 4-week follow-up, an email is sent to participants, who answer at home. To ensure high data completion, an email reminder is sent if no reply is received within 3–5 days. Further, participants are called by phone if there is no reply to the reminder email.

Functional performance

Patients' aerobic capacity is estimated during a submaximal work rate bicycle test.[60] Patients pedal until they reach a steady state, with a stable pulse rate ranging between 120 and 170 bpm, normally within 6–7 min.[60] Participants' aerobic capacity is estimated from work rate and stabile pulse rate by the use of Åstrand's Nomogram.[60]

Maximal isometric knee extension and hip abduction strength will be tested using dynamometry (JTECH medical, Commander Echo, Salt Lake City, Utah, USA). A suction cup is mounted on a door behind the examination couch. A strain gauge, measuring pull in Newton, is placed in between the suction cup and a fixation belt strapped around the participant's ankle above the lateral malleoli. For knee extension, participants sit on an examination couch with a hip angle of 90° and a knee angle of 90°. Participants are asked to press against their foot the belt in a forward motion. The distance from the knee joint axis to the middle of the fixation belt is measured. Consequently, isometric muscle strength is measured as torque. For hip abduction, participants lie on the couch with the tested leg straight and are asked to press the lateral malleoli against the belt. The distance from the trochanter major on the femoral bone to the middle of the fixation belt is measured. One practice trial is allowed and thereafter three maximal contractions are performed separated by a 60 s pause. Isometric muscle strength is normalised to body weight to increase comparability. The methods for assessing isometric muscle strength have been adapted from Thorborg *et al*[61] who reported good intertester reliability with an interclass correlation coefficient ranging from 0.76 to 0.95 and SE of measurement between 5.0% and 10.4% for hip and knee strength assessments.

Physical function is assessed by five performance tests: (1) single limb mini squats,[62] (2) number of knee bendings on one leg during 30 s standing,[63 64] (3) number of chair stands during 30 s,[6 66] (4) 40 m fast-paced walking test[65] and (5) one leg hop for distance.[63] All performance tests have been found valid to assess lower extremity function in different patient groups with knee or hip

problems.[63 66–68] As large variation regarding age and function within participants of this trial is expected, a test battery with a wide range of difficulty of the performance tests is therefore chosen to ensure that all participants would be challenged. A floor effect may be evident in the one leg hop for distance test as some participants may not be able to hop at all. No ceiling effects are expected for any of the functional performance measures.

Explanatory outcomes and nested qualitative study

To investigate how the physical environment and other potential context factors, such as participant and practitioner interaction and behaviour, may interact and mediate the treatment effects, explanatory outcomes are included. Explanatory outcomes have been selected to explain the process by which context effects work and possibly elucidate which elements within the physical environment enhance treatment effects and how these elements affect the patients and practitioners. A qualitative study will be embedded within the randomised controlled trial (RCT) design. The aim of the qualitative study is to investigate how the participants experience the two different physical environments. Observation is performed in both rooms during exercise sessions to describe and identify behaviour of practitioners and participants specific to the different physical environments. Focus group interviews will be conducted with participants to investigate their experiences with the exercise environments and to invite participants to articulate and elaborate on their thoughts on how the physical environment has affected them. Three focus group interviews will be conducted with a total of 10–20 participants from the contextually enhanced physical environment and three focus group interviews with a similar number of participants from the standard physical environment, that is, six focus groups in total. Participants invited to the focus groups will be those randomised to exercise in the RCT design (group EX+ROOM and group EX). The interviews will be transcribed and analysed using thematic coding comparing within and across the different physical environments. Additionally, in-depth individual interviews will be performed with six participants. To ensure the blinding of participants throughout the study, all interviews will be conducted after the intervention and after follow-up testing has been completed.

Additionally, a patient-reported outcome 'participant satisfaction' is reported as participants' satisfaction with the exercise intervention in itself as well as satisfaction with specific contextual factors within the physical environment. Eleven single items scoring the different factors of the physical environment, such as lighting, cleanliness, access, decoration, etc, are administered to participants in intervention groups EX+ROOM and EX. The items are adapted from Tsai *et al*.[69] Satisfaction is scored on a five-point Likert scale ranging from 1 to 5 (1=strongly dissatisfied, 2=dissatisfied, 3=fair, 4=satisfied and 5=strongly satisfied).

Compliance and adverse events

In the two exercise groups, compliance is considered good at 75% or if 12 of 16 possible exercise sessions are attended. Participants in the WL group are asked at 8 weeks follow-up whether they have started any exercise courses within the past 8 weeks. If answering yes, they are asked to describe the change. This is done in order to account for compliance to the WL design. Self-reported adverse events occurring in between exercise sessions are recorded at 4 and 8 weeks in the online survey. Adverse events are defined as any events that the participants found were restricting them physically, mentally or socially. Participants also indicate whether they have been in contact with either their general practitioner or the hospital in relation to their adverse event. Any adverse events occurring during the exercise sessions are recorded by the supervising instructors.

Randomisation

Randomisation is performed immediately after baseline assessment and is administered by a research coordinator not otherwise involved in the study. Patients are consecutively assigned and given a numbered, sealed opaque envelope entailing treatment allocation. The randomisation sequence is computer-generated and prepared by a statistician with no clinical involvement in conducting the trial. To avoid imbalances in treatment allocation among people with knee and hip pain, two block randomisation lists were computer-generated (with a 2:2:1 allocation). The block size is kept secret to maintain blinding; each block consisted of either 5 or 10 patients. The randomisation lists and envelopes are kept in a secure location at the university.

Blinding procedure

Participants are blinded to the study aim in order to avoid excess focus on the physical environment, which potentially could exaggerate context effects from the physical environment. Participants are therefore informed that they are participating in a study evaluating the effects from exercise compared with being on a WL and are not aware that the true aim of the study is to investigate the possible additional effect from an enhanced physical environment on exercise. The instructors supervising the exercise sessions are also not informed about the true aim of the study. However, they are aware that exercise sessions are performed in different rooms as they supervise sessions in both rooms. The instructors have been informed that the different exercise rooms are used for practical and logistic reasons. The primary investigator conducting baseline and follow-up testing is also blinded to treatment allocation, and participants are instructed to not to speak about the intervention with the investigator, thereby keeping blinding intact.

Sample size estimation and power considerations

This study is designed as a superiority trial with three groups (EX+ROOM, EX and WL). Since this is the first

study to investigate the additional effect of an enhanced physical environment on the effect of exercise therapy as treatment for knee or hip pain, there are no previous data on which to base our sample size estimation. Thus, the power calculation is based on factors such as feasibility, that is, how many participants will be realistic to include with the recruitment period and pragmatic issues such as availability and capacity of the different exercise rooms. Taking these aspects into consideration, 100 participants will be included in the trial. To be able to account for the natural disease progression or regression towards the mean, the WL is included in the design. A randomisation with a 2:2:1 allocation is chosen, and thus 40 participants are randomised to the EX+ROOM and EX groups, respectively, and 20 participants are randomised to the WL group. We anticipate that individuals in the WL group will experience limited effect. With 40 participants in each of the two exercise groups (EX+ROOM and EX), we are able to detect a difference of 0.75 on the GPE scale ranging from −3 to 3 with a SD of 1.2, a p value of 0.05 and a power of 80%.

Statistical evaluation

All three intervention groups (EX+ROOM, EX and WL) will be examined for comparability at baseline with respect to demographic factors using analysis of variance (ANOVA) and χ^2 test as appropriate.

The primary analysis on the GPE data will be conducted with a Student unpaired t test comparing the EX+ROOM intervention group with the EX intervention group at the 8-week follow-up. The Bonnet-Price median test will be conducted if assumption of normality in the GPE data is not supported. The WL intervention group is considered a reference group describing the natural progression of disease for the included study population and is not included in the primary analysis. However, to check the general assumption that exercise is more effective than no intervention, an unpaired t test is conducted to compare the exercise groups with the WL.

The secondary outcomes, the KOOS/HOOS, SF-36, ASES and physical function outcomes, are analysed as repeated measures (ie, change from baseline over 4 and 8 weeks follow-up for patient-reported outcomes and baseline to 8-week follow-up for physical function tests) applying a mixed linear effects model with 'participant' as the random effect and sex, age and joint as fixed effects. As for the primary outcome, only the EX+ROOM and EX groups are compared. Additionally, to test an a priori hypothesis of a graded relationship between groups EX+ROOM>EX>WL, a linear test for trend will be conducted as an explanatory analysis on all outcomes. A χ^2 test for trend is applied for dichotomous outcomes and a linear test for trend is applied for continuous outcomes. Pairwise comparison of groups will be conducted if the trend test was significant, to describe the association between group and outcome, that is, EX+ROOM versus EX and EX versus WL. For dichotomised outcomes, a χ^2 test is applied, and for continuous outcomes ANOVA is applied.

Intention-to-treat analysis is performed and the last observation is carried forward for missing data at follow-up for secondary outcomes. The primary outcome is a transition score, which is not assessed as baseline. For any participants lost to follow-up, GPE data will be missing. Further, a per-protocol analysis is conducted including only those with good compliance with the exercise intervention (participated in at least 12 of 16 sessions) in the EX+ROOM and EX groups, respectively.

A detailed statistical analysis plan will be drafted and approved by all authors before being made publicly available prior to breaking the randomisation code and conducting data analysis. To further minimise the risk for bias introduced during analysis and interpretation, data analysis will be performed by a third party not otherwise related to the study. Intervention groups will be allocated with arbitrary names. Interpretation will be performed by the primary investigator in collaboration with the research team prior to revealing treatment allocation, thereby interpreting the results blindly.[70] Consequently, two interpretation scenarios will be drafted on the basis of the primary outcome data, that is, comparing treatment A with treatment B, one assuming that group A will be the EX+ROOM group and the other assuming that A will be the EX group.

ETHICS AND DISSEMINATION

The findings of this study will be disseminated though peer-reviewed publications and through international conference presentations.

The primary ethical concern in this study is that the true aim of the study is withheld from participants. Withholding the aim disables participants from considering the implications of the research and from assessing whether or not they want to contribute to the investigation of this aim. However, blinding the true aim is imperative to the study design as an effect from the physical environment may be overestimated or underestimated if participants are explicitly made aware of the actual aim of the study. Participants are therefore told that the study is designed to investigate the effect of neuromuscular exercise as an early treatment strategy for musculoskeletal pain. Similarly, the supervising instructors are also blinded to the true aim of the study. The instructors are aware that the exercise is performed in different environments, but they are told this due to logistic reasons. The ethics committee has been explicitly made aware that study participants and instructors are not made aware of the true study aim and despite this sanctioned the study without any reservations or conditions.

DISCUSSION

Context effects may constitute an important part of the effects of exercise therapy. Investigating context effects will provide knowledge on how the physical environment

may be exploited to enhance the effects of exercise therapy in addition to the effect of the specific exercise. Exercise is an effective and widely used core treatment strategy for chronic diseases, such as musculoskeletal disorders, cardiovascular disease and diabetes. Adding to the effect of exercise through context effects from a contextually enhanced physical environment in exercise facilities may be highly beneficial for patients across a number of diseases.

Previous research in context effects from physical environments has been conducted in hospital settings.[27] A comprehensive review from 2008 showed that certain elements within a hospital context, such as noise and lighting level, have an impact on the number of medical errors as well as increased pain and stress levels for patients and staff. [27] Research in other healthcare settings has been sparse. During an initial literature review, only one study was identified as having investigated physical therapy and its relation to the physical environment. The literature review comprised groups of search terms for context effects, exercise/physical therapy and terms for physical environments. Articles were searched for in MEDLINE, Scopus and single-specific journals such as the *Health Environment Research and Design* journal. When reviewed, this single study used observation, surveys and interviews to learn more about the design of a hospital rooftop garden rather than investigating if the physical environment had an additional effect on the physical therapy.[71] Further, the therapy of the study was described as activities including gardening, golf putting and events such as concerts or barbeques, not regular exercise. Consequently, this is, to the best of our knowledge, the first study to investigate if there is an effect from an enhanced physical environment in addition to exercise when compared with exercise performed in a standard setting.

The three-armed RCT design of the present study has several advantages. It has been widely discussed whether the placebo effect can be explained by spontaneous remission or regression towards the mean.[15 72–74] To rule out either of these as explanatory factors of a possible effect, the WL group is included in the design as an untreated reference group. The WL group illustrates the natural course of disease for the study population during the study period. Consequently, if a difference is seen between the two exercise rooms, the WL group enables an assessment of whether the difference is caused by spontaneous remission by comparing the exercise groups to the WL. To optimise the number of study participants, a 2:2:1 allocation with half the number of participants allocated to the WL is chosen. The three-armed design also allows for a test for trend across groups. This form of analysis has been previously applied in a study investigating context effects originating from patient and practitioner interaction.[44]

Context effects are a multifactorial concept and several factors, other than the physical environment, may contribute to the context effect of a given treatment. Literature reviews on context effects have additionally suggested factors, such as characteristics of patients/participants, practitioner/instructors or treatment and nature of disease, as potentially contributing to the total context effect, and theoretically components may interact and possibly have synergistic effects.[8 9 16 24 75] Especially the interaction between patient and practitioner has been suggested as a significant contributor to context effects.[44 76–85] In a recent study, Kaptchuk *et al*[44] found that patients with irritable bowel syndrome, who were treated by a warmer and friendlier practitioner, had significantly better results from sham acupuncture than those treated by a practitioner, who limited eye contact and avoided conversation. Similarly, Suarez-Almazor *et al*[83] found that patients with knee OA treated with sham acupuncture by a practitioner, who expressed high expectations to the treatment, had better outcomes than those treated by a practitioner with a neutral position towards treatment effects. Although interaction between the patient and the practitioner is suggested as the most robust component of context effect, behaviour, communication and interaction between patient and practitioner are difficult to change and may be hard to reproduce. An advantage in exploiting the potential context effect from the physical environment is that the components of the environment can be thoroughly described and more easily implemented or changed in existing exercise environments.

There are some limitations to the study design that must be acknowledged. The multifactorial concept of context effects questions whether the physical environment can be isolated and studied alone. Several actions are taken to isolate the physical environment as the only difference between groups in this trial. The exercise programme is standardised and delivered in a group fashion by the same instructors, and all instructors have supervised in both physical environments. Consequently, treatment characteristics are similar between the intervention groups. Participants' characteristics, known and unknown, should be equally distributed between groups as a result of the randomisation process. Any specific characteristics that may originate from the instructor or from instructor–participant interaction should also be comparable between groups, as instructors supervise in both rooms.

Additionally, the nested qualitative study is aimed at investigating how the physical environment may affect the behaviour of the participants or instructors or the interaction between them. The study will elucidate these issues and help explain the process of how a standard and enhanced physical environment affects participants and instructors.

This study is designed to investigate the significance of the physical environment for the effects of exercise therapy and rehabilitation. The design of the study is novel and the results will provide knowledge on the significance of creating an optimal context for exercise therapy. Further studies investigating context effects of treatment are warranted to further enhance treatment effects.

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Competing interests None.

Ethics approval The Regional Scientific Ethical Committee for Southern Denmark has approved the study (study ID: S-20130130). It is consistent with the Helsinki Declaration and registered with http://www.clinicaltrials.gov (ID: NCT02043613).

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Paper II

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Osteoarthritis and Cartilage

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Brief Report

Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain

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SUMMARY

Objective: Patients considering or engaged in exercise as treatment may expect or experience transient increases in joint pain, causing fear of exercise and influencing compliance. This study investigated the pain trajectory during an 8-week neuromuscular exercise (NEMEX) program together with acute exercise-induced pain flares in persons with knee or hip pain.

Design: Individuals above 35 years self-reporting persistent knee or hip pain for the past 3 months were offered 8 weeks of supervised NEMEX, performed in groups twice weekly. The program consisted of 11 exercises focusing on joint stability and neuromuscular control. Participants self-reported joint pain on a 0–10 numerical rating scale (NRS) at baseline and 8-weeks follow-up. NRS pain ratings were also collected before and immediately after every attended exercise session.

Results: Joint pain was reduced from baseline (NRS 3.6; 95% CI 3.2–4.1) to 8-weeks follow-up (2.6; 95% CI 2.1–3.1), ($P < 0.01$). Pain decreased 0.04 NRS (95% CI 0.02–0.05, $P < 0.01$) on average per exercise session and pre- to post-exercise pain decreased 0.04 NRS (95% CI 0.03–0.05, $P < 0.01$) on average per session, approaching no acute exercise-induced pain in the last weeks.

Conclusion: This study found a clear decrease in size of acute exercise-induced pain flares with increasing number of exercise sessions. In parallel, pain ratings decreased over the 8 weeks exercise period. Our findings provide helpful information for clinicians, which can be used to educate and balance patient expectation when starting supervised neuromuscular exercise.

Introduction

Exercise is effective for relieving lower extremity joint pain[1,2] and recommended as first-line treatment in clinical guidelines for osteoarthritis (OA) treatment[3]. However, patients with lower limb joint pain may experience increased pain during physical activity or exercise and may therefore be hesitant to participate in exercise treatment[4]. Furthermore, joint pain may fluctuate over the course of an exercise intervention period. Knowledge about the trajectory of joint pain during an exercise treatment would be important knowledge for both clinicians and patients; as such information could influence patients' compliance with the exercise therapy. Patients may be more willing to accept transient increases in joint pain during exercise, if knowing what to expect.

There are no specific recommendations regarding type of exercise for treating musculoskeletal pain such as OA. However, exercise programs that are supervised and have specific aims relief pain more effectively than unsupervised or generic exercise programs[5]. Neuromuscular training, such as the neuromuscular exercise (NEMEX) program, has previously been proven feasible, well tolerated and effective in relieving joint pain and improving function in different populations with knee or hip pain[6–8]. The NEMEX program is an individualized and goal-based program focusing on lower-limb alignment and functional stability during movement[7].

The study aimed to investigate the trajectory of joint pain during an 8 week NEMEX program together with the acute pain flare evoked from each exercise session in middle-aged individuals with knee or hip pain.

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Methods

This study presents ancillary data to a randomized controlled trial (RCT) investigating context effects in exercise (ClinicalTrials.gov identifier NCT02043613). As the current study investigates pain trajectory in relation to exercise, only the exercise groups from the RCT have been included. Ethical approval was obtained by The Regional Scientific Ethical Committee for Southern Denmark (S-20130130). All participants gave their written informed consent.

Participants were recruited through newspaper advertisements, social media and through referrals from general practitioners or the orthopaedic department at Odense University Hospital. Eligibility criteria: men and women aged 35 years or older, self-reporting persistent knee or hip pain for the past 3 months, willingness and ability to participate in exercise program twice weekly. Exclusion criteria: co-morbidities prohibiting exercise, not reading or understanding Danish or already attending structured supervised exercise or other treatment aimed to relieve joint pain. Participants were examined at baseline to assess clinical signs of knee or hip OA, respectively[9] although this was not a specific entry criteria.

NEMEX

All participants were offered 8 weeks of NEMEX. The NEMEX program is based on biomechanical and neuromuscular principles aiming to improve sensorimotor control and achieve functional stability[7]. The exercise program is structured with a 5–10 min warm-up on an ergometer bicycle followed by 11 specific exercises focusing on core stability, postural function and orientation, lower limb muscle strength and functional tasks[7]. All exercises were performed with 2–3 sets with 10–15 repetitions. Every exercise had four levels and participants progressed when performing an exercise at its current level with good movement quality and sufficient volume. Sessions were performed in groups, lasting 1 hour and were supervised by certified instructors. Participant's attendance was registered at each exercise session. Good compliance was defined as attending 75% or more of the exercise sessions.

Pain measures and registration

Self-reported pain was assessed for the index joint using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain)[10]. Participants rated their pain for the index joint at the baseline visit and at the 8-week follow-up, when the exercise period was completed. Additionally, participants rated joint pain in an exercise diary before and after every exercise session they attended. Pain was accepted during exercise and was used to monitor and guide progression and regression in exercise levels during the 8-week exercise period. Pain from 0 to 2 was considered safe, from 3 to 5 was acceptable and pain above five was categorized as high-risk. If participants were reporting pain within the high-risk range, exercise volume or level was reduced to suit the individual at the next exercise session[7].

Statistics

A Student's paired *t*-test was used to compare difference in joint pain from baseline to 8 weeks follow-up. To check if compliance had any effect on the pain relief from exercise an unpaired Student's *t*-test was used to compare change in pain from baseline to follow-up between the compliant and non-compliant groups.

Pain ratings from the 16 exercise session were used in the pain trajectory analysis. Linear regression analysis was performed to investigate pain trajectory over time, using the group mean pre-exercise pain ratings from each individual exercise session as dependent variable and time as independent variable. Similarly, linear regression was performed to investigate the acute pain flare evoked by the individual exercise session (i.e., group mean difference in pain between before and after each of the 16 exercise sessions) (dependent variable) during the exercise period (independent variable). *P*-values of <0.05 were considered statistically significant.

Results

In total 82 participants were offered the NEMEX program in the RCT trial; three participants never started the exercise program and one exercise diary was lost. These four participants were excluded from this study. The remaining 78 participants (46 women) had a mean age at baseline of 58.6 years (standard deviation 10.4) and a mean Body Mass Index (BMI) of 28.1 (5.3). Forty-nine participants reported the knee as the primary site of pain. Of these 36 had clinically diagnosed knee OA[9]. The hip was the primary site of pain in 29 participants, of which 10 had clinically diagnosed OA[9]. One participant was lost to follow-up.

Joint pain was reduced by 1.0 NRS (95% CI 0.5–1.6) from 3.6 at baseline (95% CI 3.2–4.1) to 2.6 NRS (95% CI 2.1–3.1) at 8 weeks follow-up ($P < 0.01$), (Fig. 1). When dividing the group into compliant ($n = 52$) and non-compliant ($n = 25$), there was no significant difference in pain relief between the groups ($P = 0.09$). The compliant group had a pain reduction of 1.3 NRS (95% CI 0.8–2.0) and the non-compliant had a reduction of 0.4 NRS (95% CI −0.7 to 1.6). No differences were found in age, sex, BMI or pain at baseline between the compliant and non-compliant groups.

In total 98.5% of all possible pre-exercise pain ratings were available in the dataset. Number of participants contributing with data at the different time-points is reported in Fig. 1. A clear relationship was observed between time (i.e., increasing number of exercise sessions) and pre-exercise pain. The pain level decreased over time with 0.04 NRS per exercise session (95% CI 0.02–0.05, *P*-value <0.01). Time (i.e., increasing number of exercise sessions) explained 64 % ($r^2 = 0.64$, $P = 0.00$) of the change in pain level (Fig. 1).

In total 97.2% of all possible pre-to post-session pain ratings were available. The number of participants contributing with data at the different time-points is reported in Fig. 2. The acute pain flare evoked by an exercise session decreased over time by 0.04 NRS per

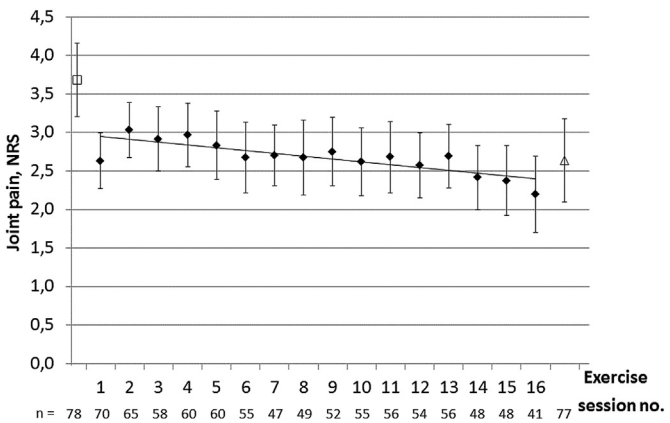

Fig. 1. Mean pain ratings (black diamonds) immediately before the 16 individual exercise sessions within the 8 week exercise period, at baseline examination (white square) and at 8 weeks follow-up (white triangle). Error bars are 95% confidence intervals. *n* = number of participants with available data at the specific time points. NRS, ranging from 0 to 10, best to worst.

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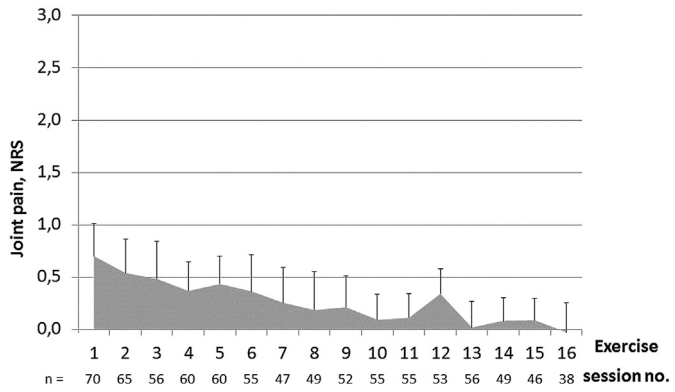

Fig. 2. Increase in acute pain from before to immediately after each of the 16 exercise sessions within the 8 week exercise period (gray area). Error bars are 95% confidence intervals. n = number of participants with available data at the specific time points. NRS, ranging from 0 to 10.

session (95% CI: 0.03–0.05, P-value <0.01). Time (i.e., increasing number of exercise sessions) explained 84 % ($r^2 = 0.84$, $P = 0.00$) of the variation in size of acute pain flare (Fig. 2).

Discussion

Patients with knee or hip pain reported a pain reduction of 1.0 NRS from the baseline visit to 8 weeks follow-up of twice weekly, supervised NEMEX. The pain trajectory decreased linearly over the 8-week exercise period. Similarly, the acute pain flare from an exercise session gradually decreased over time and approached no flare at all during the last weeks of the 8-week period.

The 1 point NRS pain reduction from baseline to 8-week follow-up corresponds to an effect size of 0.48 (95% CI: 0.16–0.80), which is in line with effect sizes reported in recent meta-analyses on exercise as treatment for knee and hip OA[1,2]. The effect size is also similar to what has been reported previously in a study investigating pain relief from NEMEX in patients with lower limb OA awaiting total joint replacement[8]. The minimal clinical important improvement has been reported to be 1 NRS-point (corresponding a 15% change) in a population with chronic musculoskeletal pain[11] and in patients with painful knee or hip OA[12]. However, another study including patients with a variety of conditions such as diabetic peripheral neuropathy and post-herpatic neuralgia, OA, chronic low back pain and fibromyalgia, reported a 2-point reduction (30% change) as a clinical important improvement in NRS pain[13]. The 1.0 NRS-point (95% CI 0.5–1.7) improvement observed from baseline to 8-weeks follow-up in this study corresponded to a 27% improvement in pain and an effect size of 0.48 which we consider a clinical important improvement given the population in this study.

To our knowledge, this is the first study to investigate the pain trajectory in participants attending neuromuscular exercise therapy for knee and hip pain. A major strength of this study is the high resolution of pain ratings, including pain ratings not only at baseline and follow-up but also from all 16 exercise sessions. Pain ratings from before and after exercise have previously been reported, however only as a median for all exercise sessions during an exercise period, rather than separately for each exercise session. These studies found no differences in pain before and after exercise for patients with severe knee or hip OA awaiting total joint replacement[7,14].

Information that regular physical activity and individualized exercise can reduce joint pain and improve physical function has the highest priority, when informing patients with knee or hip OA about their disease[15]. However, patients may feel hesitant to start exercise because of fear of increased joint pain as a result of exercise[4]. The average pain flares within the first 2 weeks was 0.79 NRS for the non-compliant group, compared to 0.43 NRS in the compliant group, ($P = 0.046$). This difference in initial pain flares may have affected compliance. This study provides detailed information on the magnitude and direction of pain relief, which can be expected from neuromuscular exercise for patients with knee and hip pain. This information is important for clinicians, who can inform patients that small transient pain flares from exercise should be expected starting exercise treatment; however the pain flares diminish over time and should not be expected with exercise after 6–8 weeks. This may motivate patients to start and be compliant with exercise treatment in spite of initial pain flares.

It is a limitation to this study that a comparison of pain trajectories for exercising participants and passive controls is not possible, as the waiting-list group in the RCT did not register pain during the 8 weeks. However, there was no difference in pain at baseline and follow-up for the RCT's waiting-list group ($P = 0.55$). It is also a limitation that all participants did not undertake all 16 exercise sessions. It cannot be eliminated that some participants stopped early because of pain. Similarly, the number of participants included in the regression analyses at the specific exercise sessions decreased with time (see Figs. 1 and 2). Both factors could create a selection bias potentially overestimating the decrease in acute pain flare with increased number of exercise sessions. However, all participants took part in the follow-up examination where a pain decrease was seen, thereby making this scenario less likely. Also, persisting self-reported pain was an inclusion criterion, but no predefined cut-off for NRS pain was used. Consequently, participants with both very little and very severe joint pain could be included in the study. Mean pain at baseline corresponded to mild to moderate pain.

In conclusion, this study found a clear decrease in size of acute exercise-induced pain flares with increasing number of exercise sessions. In parallel, pain ratings gradually decreased over the 8 weeks exercise period. This study provides detailed information about the pain trajectory during exercise treatment. This information is helpful for clinicians as it can help educate and balance patients' expectations when starting supervised neuromuscular exercise as treatment for knee and hip pain.

Contributions

LFS, ER and JBT were all involved in the design of the study. All authors contributed to drafting the manuscript or revising it. All authors read, commented and approved the manuscripts for publication. LFS is the trial manager and responsible for coordinating and conducting the study. SJB supervised the exercise intervention, performed data collection and data entry. LFS screened, included and performed all baseline and follow-up testing.

Role of the funding source

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Competing interests

The authors have no competing interests to declare.

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Paper III

Influence of the physical environment on the effect of exercise therapy for knee and hip pain –

A mixed-method randomized controlled trial

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Abstract

Importance: Good patient-practitioner relations are known to positively affect treatment outcomes, but are difficult to standardize across settings. The physical environment in which treatment is delivered may also influence health outcomes and is easier to standardize.

Objective: To investigate the influence of the physical environment on the treatment response to exercise therapy.

Design: A mixed-method randomized controlled double-blind clinical trial.

Setting: Exercise therapy facilities.

Participants: Middle-aged individuals reporting persistent knee or hip pain within the past three months. 103 participants were randomized 2:2:1; 42 to exercise in a contextually enhanced environment, 40 to exercise in a standard environment and 21 to a passive waitlist.

Interventions: Eight weeks of group-based neuromuscular exercise therapy supervised by the same therapists, blinded to the study aim, and performed in either a newly built contextually enhanced environment, or a standard old, unenhanced environment. The passive waitlist group received no intervention prior to follow-up.

Main outcome and measures: The primary outcome measure was participants' Global Perceived Effect (GPE) rated after 8 weeks on a 7-point Likert scale ranging from '[-3] markedly worse through '[0] no change' to '[3] markedly improved'. The study included 6 nested focus groups with participants (n=25) and individual interviews with therapists (n=2) exploring experiences and perceptions of the physical environment.

Results: Mean age was 58.5 years, 61% were women, and 63% complained primarily about their knee. As expected, the waitlist group reported no significant improvement (-0.05 GPE CI 95% -0.5 to 0.4). Contrary to our hypothesis, the group exercising in a standard environment had greater improvement (0.98, CI 95% 0.5 to 1.4) than the group exercising in the contextually enhanced

environment (0.37, CI 95% -0.2 to 0.9), p=0.07. Secondary outcomes, per protocol analysis and qualitative findings supported the primary finding. In the standard environment, subjects felt at-home, a greater sense of fellowship and identified themselves with the worn room as it reflected their own body image.

Conclusion and relevance: The study results indicate that the physical environment does influence treatment effects from exercise therapy, and suggest that matching the exercise environment to the users' preferences may result in greater patient-reported treatment response.

www.clinicaltrials.gov identifier: NCT02043613

Keywords: context effect, physical environment, exercise therapy, neuromuscular exercise

Introduction

Context effects are defined as the effects of a given treatment, not caused by the treatment itself, but rather by the context in which treatment is given[1-3]. Previous studies have focused on the patient-practitioner relationship as the main contributor to context effects, showing, for example, that patients treated by empathetic practitioners achieve larger treatment benefits[4-6].

Factors within the built hospital environment, such as insufficient lighting intensity, daylight deprivation and elevated noise levels, affect health negatively[7-9]. Environmental factors can also affect health positively[7,10,11] and may be used to enhance treatment effects[12]. However, it is unknown how the physical environment influences health outcomes from treatments in settings other than hospitals, such as rehabilitation and exercise facilities, or to what extent the environment in which an intervention takes place influences the outcomes achieved. The aim of this study was to investigate the physical environment as a contributor to context effects in exercise therapy, a potent intervention for chronic diseases such as cardiovascular disease, diabetes, and musculoskeletal disorders[13,14].

Methods

Study design

This was a 3-armed double-blind randomized controlled clinical trial (RCT). The detailed study protocol has been published[15].

The study was approved by The Regional Scientific Ethical Committee for Southern Denmark (S-20130130), registered at ClinicalTrials.gov (NCT02043613) and complies with the Helsinki Declaration. After giving written consent, participants were consecutively randomized according to a computer-generated list in a 2:2:1 allocation to either 1) exercise in a contextually enhanced environment, 2) exercise in a standard environment or 3) a waitlist. Participants and therapists were blind to the study aim, which was to investigate the influence of the physical environment. The outcome assessor and the third party performing data analysis were blind to treatment allocation.

Participants

Recruitment was undertaken through posters and informational leaflets at general practitioners offices or participant initiated contact via posters and articles in local newspapers and social media. Eligible participants were 35 years or older, self-reporting persistent knee or hip pain within the last 3 months, and who were willing and able to attend exercise therapy twice weekly at the University of Southern Denmark, Odense. Exclusion criteria were: 1) Co-morbidities or contraindication prohibiting exercise therapy; 2) Inability to speak, read or understand Danish; 3) on-going participation in exercise therapy aimed specifically at relieving knee or hip joint problems; 4) surgery to the hip/knee within 3 months or awaiting joint surgery.

Intervention

Physical environments

Differences between the two exercise-environments are detailed in Table 1 (see pictures in eMethod). The major differences were in the location of the rooms, and their age and appearance. The contextually enhanced environment appeared new and modern, whereas the standard environment appeared old and worn.

Exercise therapy program

The same standardized NEuroMuscular EXercise (NEMEX) program was used in both exercise groups[16]. NEMEX has been proven effective to relieve pain and improve function in populations with knee or hip pain[16,17]. Exercise was performed in groups, lasted one hour and was supervised by therapists certified in delivering the exercise program. The same therapists supervised the exercise therapy in both environments to ensure consistency of supervision and therapist between groups.

Waitlist

Participants randomized to the waitlist were on a passive waitlist for 8 weeks. This group acted as an untreated control group.

Baseline and follow-up assessment

Clinical examinations and demographics were recorded at baseline. Primary outcome data were obtained at 8-week follow-up. Patient-reported outcomes were collected at baseline, 4-week and 8-week follow-up. Functional performance tests were assessed at baseline and 8-week follow-up.

Outcome measures

The pre-specified primary outcome was participants' Global Perceived Effect (GPE) [18,19], a transition score assessed at 8-weeks follow-up. Participants responded to the following question;

"Compared to when entering the study, how are your knee/hip problems now?" on a 7-point Likert scale. The GPE scale ranged from '[-3] = markedly worse' through '[0] = no change' to '[3] = markedly improved'.

Secondary outcomes were change from baseline to 8-week follow-up in patient-reported outcomes and functional performance tests. The patient-reported outcomes included: the joint-specific questionnaires the Knee injury and Osteoarthritis Outcome Score (KOOS) or The Hip disability and Osteoarthritis Outcome Score (HOOS) depending on the location of joint pain[20,21], the Short Form Health Survey (SF-36)[22,23], a modified version of Arthritis Self-Efficacy Scale (ASES)[24] and participants' stress level and satisfaction with the exercise therapy and physical environment[25]. Functional performance tests included; 1) single limb mini squat[26], 2) number of knee bends on one leg during 30 sec[27], 3) number of chair stands during 30 sec[28,29], 4) 40 m fast-paced walking time[28] and 5) one leg hop for distance[27]. Aerobic capacity and maximal isometric strength for knee extension and hip abduction were also assessed.

Compliance for the two exercise groups was considered good if 12 of 16 possible exercise sessions were attended. Adverse events occurring in-between exercise sessions were self-reported at 4 and 8 weeks in the online survey. Adverse events occurring during the exercise sessions were recorded by the supervising therapist.

Embedded qualitative interviews

Three focus group interviews were conducted on a convenience sample of 12 participants from the standard environment and 3 focus-groups with 13 participants from the contextually enhanced environment. Topic-guides focused on experiences and perceptions of the environment. A photo-elicitation technique was used to focus participants' dialogue on the environment in which the exercise intervention took place[30,31]. Face-to-face interviews with 2 consecutive therapists

supervising in both environments explored their experiences and perceptions. Interviews took place after participants had completed their 8-week follow-up to ensure maintenance of blinding. Interviews were conducted between December 2014 and March 2015. Focus-group interviews lasted between 71-104 minutes; face-to-face interviews lasted 64 and76 minutes. Interviews were audio-recorded, transcribed verbatim and anonymized with participants' written consent. Interview data were coded thematically using deductive and inductive codes. Data was analyzed using the Framework approach[32]. Themes were identified and compared within and across the two exercise environments. Qualitative data were analyzed prior to analyzing quantitative data and breaking the treatment code.

Statistical analysis

Details of the sample size calculation and randomization process have been described[15]. The study was powered to detect a 0.75 difference in GPE (SD 1.2, significance level of 0.05, 80% power). A statistical analysis plan was completed and made publicly available at the University website prior to conducting data analysis[33]. Analysis for the primary outcome was performed by a blinded independent third party. To reduce the risk of bias the authors agreed in writing on two alternative interpretation scenarios prior to breaking the randomization code[34].

Data were checked for normality at baseline. The primary endpoint was a Student's unpaired t-test comparing GPE scores between the contextually enhanced environment and the standard environment at the 8-week follow-up. A linear test for trend was performed across all groups to explore the a-priori hypothesis of a graded relationship between groups: waitlist < standard environment < contextually enhanced environment. A per-protocol analysis was performed including participants attending 12 of 16 possible exercise sessions or more. Secondary analyses on the patient-reported outcomes and functional performance tests were performed as repeated

measures using a multilevel mixed-effect model with participants as random effects, time, group and interaction between time and group as fixed effects. All available data points were included.

Results

Enrolment

In the period from February to November 2014, a total of 103 participants were randomized: 42 to the contextually enhanced environment, 40 to the standard environment and 21 to the waitlist group (Fig.1). One participant in the contextually enhanced environment and 1 in the waitlist were lost to follow-up at 8 weeks for the primary outcome.

Participant characteristics

All groups were comparable across participant characteristics at baseline (Table 2). The mean age of the study population was 58.5 years (standard deviation 9.9 years), 61% were women, 63% primarily complained about their knee, 88% reported pain for more than 1 year and 59% had clinically diagnosed osteoarthritis of the knee or hip according to the American College of Rheumatology criteria[35]. All groups were comparable across all study outcomes at baseline (see eTable 1).

Primary outcome

The waitlist group reported no significant improvement (-0.05 GPE CI 95% -0.5 to 0.4), whereas both exercise groups combined significantly improved compared to the waitlist group, p=0.05. Contrary to our hypothesis, the treatment response was greater in the standard environment (0.98, CI 95% 0.5 to 1.4) compared to the contextually enhanced environment (0.37, CI 95% -0.2 to 0.9), p=0.07. The test for trend across groups in the a-priori hypothesized order (waitlist < standard environment < contextually enhanced environment) was thus insignificant (p=0.36). For the per protocol analysis, including participants attending at least 12 of 16 possible sessions, the treatment response was greater, indicating a positive relation between dose of exercise and treatment

response, and similarly favored the standard environment (standard environment 1.3, CI 95% 0.9 to 1.7, contextually enhanced environment 0.8 CI 95% 0.3 to 1.4, p=0.20).

Secondary outcomes

Patient-reported secondary outcomes evaluating symptoms, function and quality of life related to the joint and self-efficacy supported the primary finding of a greater treatment response to exercise therapy in the standard environment. However, there was no difference between groups in treatment response in objectively assessed aerobic capacity or knee extensor muscle strength after exercising in the two different environments. Improvement in the knee bending performance test was larger for participants from the standard environment. The primary and all secondary outcomes data are summarized in Fig. 2. Within group changes and between group differences are given in eTable 1. A transient exercise-induced pain flare was the most commonly reported adverse event, as shown in eTable2.

QUALITATIVE FINDINGS

The qualitative interviews provided insight into how participants reflected upon their experience of their respective exercise environments, the importance of the first impression and how it changed over time, and a sense of fellowship within a shared space.

Reflections

Participants treated in the standard environment felt that the old, worn room reflected their own physical state and did not perceive the poor appearance of the standard environment negatively. Rather they identified themselves with the room as it reflected their own body-image. Participants exercising in the standard environment felt more at-home than participants in the contextually

enhanced environment, and expressed nostalgia towards the worn room as it reminded them of their school gyms. *"I also know that it means something that you feel at-home in the place you are in and I think that I did. […]. So in that way it suited me very well, that it was a little worn. (Mia, focus group (FG)1, standard environment)"* In both environments, mirrors presented participants with a direct reflection of their bodies, providing visual feedback to improve movement quality during exercises; however participants avoided mirrors as they felt uncomfortable seeing their reflection while exercising. In general, mirrors were strongly associated with commercial gym facilities, which participants perceived as inappropriate places for exercise therapy. "*I have a phobia of mirrors. […] It's because if you do not care much about your own appearance, I think. (Hanne, FG3, standard environment)*"

Transition

Participants described markedly different experiences in their journey into the two exercise environments. Participants exercising in the contextually enhanced room described their journey positively. They ascended an open stair-case and felt they were a part of an exercise community, as the contextually enhanced environment was located in a newly built multi-purpose University Sports Science facility. Contrarily, participants exercising in the standard environment descended an enclosed staircase leading to a dark basement, which was described as unwelcoming. Several participants felt unsafe during their first transition into the room. These transitions were pivotal in participants' first positive or negative impression of their respective exercise environment. For the participants exercising in the standard environment this perception changed over time, as participants imbued the space with meaning and value after having positive experiences in the space, transforming the space into a therapeutic place. This change was mediated by routines, for

the participants exercising in the standard environment these routines included using ”way markers” to navigate the basement.

Sense of fellowship

An important difference in experiences was the sense of fellowship felt within each environment. In general, all participants expressed a sense of cohesion as all had joint pain and felt an obligation towards completing the research project. The study design employed, where participants continuously joined the group as they were enrolled, was perceived as interruptive across environments. In both environments, music during exercise facilitated the sense of fellowship as it provided a subject of conversation and broke the silence. The large window in the contextually enhanced room provided a positive distraction from the monotony in some of the exercises and gave participants a feeling of being part of a larger group which included those exercising outside at the purposefully designed and award-winning athletic field. Although the music and view in the contextually enhanced environment were described as positive features; they seemed to distract participants from developing positive social relationships. Participants exercising in the contextually enhanced environment explicitly stated that they did not feel part of a team, whereas participants exercising in the standard environment described a strong sense of fellowship. Without the distraction from the outside view combined with the austerity of the space, the group in the standard environment seemed more conscious of each other, and at-home in the environment.

“From my perspective it is something that motivates […] that there’s a good atmosphere. And it is only there, when we feel comfortable and safe. […] It has a contagious effect. (Tina, FG3, standard environment)”

Discussion

We compared exercise therapy performed in a contextually enhanced environment with exercise performed in a standard, old space. The treatment response was greater in the standard environment compared to the contextually enhanced environment, contrary to the hypothesized relationship. Patient-reported secondary outcomes and per protocol analyses supported the primary finding. However, the environment did not influence objectively assessed outcomes, such as aerobic capacity and muscle strength. The nested qualitative study indicated that the sense of fellowship and feeling of comfort, security and warmth was greater among participants exercising in standard environment.

To our knowledge, this is the first study to investigate the influence of the physical environment on the treatment effects in an exercise setting within a randomized controlled trial design. Previous studies performed in hospital environments have reported on single factors within the physical environment, in observational or intervention designs with only few randomized studies. Here, light intensity, exposure to daylight and view to nature scenes were reported to enhance treatment effects in postoperative patients[8,10,36]. These proposed enhancing factors from hospital environments did not produce a similar response in our enhanced exercise therapy setting. Consequently, our results suggest that the influence from the physical environment may vary across patient groups, interventions and health-care settings.

We observed greater differences in the response of patient-reported outcomes than in the functional performance tests and no differences were seen in aerobic capacity and muscle strength (Fig. 2). This finding is in line with previous studies and a systematic review which conclude that greater placebo or context effect is seen in patient-reported outcomes and in diseases defined by patient-

reported symptoms[4,37,38]. We suggest for future trials to include both patient-reported and objectively assessed outcomes to better elucidate mechanisms involved in treatment response.

Previous studies on context effects have mostly concentrated on investigation of the patient-practitioner relationship. For example, Suarez-Almazor et al. reported greater pain relief in knee osteoarthritis patients treated by a practitioner expressing high expectations of treatment effects compared to neutral expectations[5]. Kaptchuk et al. showed that a warm, empathic and confident communication style, compared to limited communication, resulted in greater symptom relief for patients with irritable bowel syndrome[4]. They concluded that the patient-practitioner relationship was the most important component of context effect. However, several other factors have been thought to contribute to context effects, such as characteristics of the practitioner, patient or treatment, severity of disease, and the environment[1,38,39]. The current and previous studies[4,5] attempt to isolate a specific factor's contribution to the context effect by applying a RCT design. As a result of the randomization, all other potential contributing factors should be equally distributed between intervention groups, thereby isolating the physical context of exercise therapy as the only difference. However, the nested qualitative study suggested that the clearest difference between exercise environments was in sense of fellowship, i.e. social relations. Consequently, we may question if it is possible to isolate a single context factor or if the context effect rather is the sum of all potential context factors intertwined.

We used a 3-armed RCT design to separate components of the observed treatment effect[38-40]. The difference between the waitlist and the combined exercise group represents the overall treatment effect from exercise therapy, whereas the difference between the two exercise groups represents the context effect originating from the physical environment. Adding a passive waitlist group excluded

the possibility that the observed treatment effect was caused by natural remission[41]. The effect size in the primary outcome was 0.49 when comparing the combined exercise groups to the waitlist group. An effect size of 0.5 is considered moderate, and is similar to what is expected from exercise therapy as treatment for knee pain from osteoarthritis [42,43]. Musculoskeletal pain is the most commonly perceived barrier to engaging in physical activity in people over 65[44,45]. Counter intuitively, exercise relieves joint pain and is a recommended core treatment for a variety of lifestyle diseases including musculoskeletal disorders[13,14].

In conclusion, this study is the first to investigate the influence from the physical environment on the response to exercise therapy in a randomized controlled design. The study results indicate that the physical environment does affect treatment outcomes, and that giving greater attention to matching the physical environment for exercise therapy to the attitudes and preferences of the intended users may enhance self-reported treatment effects from interventions such as exercise therapy.

List of abbreviations

RCT: Randomized Controlled Trial.

GPE: Global Perceived Effect

NEMEX: Neuromuscular exercise.

KOOS: the Knee Osteoarthritis and injury Outcome Score

HOOS: the Hip disability and Osteoarthritis Outcome Score

SF-36: Short-Form (36 item) Health Survey

ASES: Arthritis Self-Efficacy Scale

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Conflicts of interest

The listed author(s) have no conflicts of interest to declare.

Author contribution

LFS, JBT, RU, PD and ER were all involved in the design of the study. All authors contributed to drafting the manuscript or revising it. LFS, JBT and ER comprise the steering committee for the study. LFS was the trial manager and responsible for the coordinating and conducting the study. LFS recruited, screened and conducted all baseline and follow-up testing. LFS, PD and AM designed nested qualitative study, LFS performed all interviews, AM supervised the data collection process, AM and PD contributed to the analysis of the qualitative data. All authors read, commented and approved the manuscripts for publication.

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Figure legends

Figure 1: Screening, enrollment, randomization, intervention and follow-up.

Figure 2: Mean difference in treatment response on primary and all secondary outcomes from 8 weeks of exercise therapy between the standard environment and the contextually enhanced environment. Estimates to the left of the 0-line favour the group exercising in the standard environment, outcomes to the right of the 0-line favour the group exercising in the contextually enhanced environment. Confidence intervals crossing the 0-line indicate the difference in treatment response not being statistically significant. KOOS; Knee Osteoarthritis and Outcome Score, HOOS; Hip disability and Osteoarthritis Outcome Score, ASES; Athritis Self-Efficacy Scale, SF-36, Short Form Health Survey 36 items, VAS; visual analog scale, 100 mm, WMD; weighted mean difference, 95% CI; 95 % condificence intervals. All secondary outcomes were scaled down in an 1:10 ratio in order to ensure comparable visual proportions across outcomes with scales of different range.

Table 1: Characteristics of exercise environments	Contextually enhanced environment	Standard environment
Description	The exercise environment is located in a newly built facility on the second floor and has a vista over a sport and recreational park. The room is a designated exercise room. It appears clean and new, with rubberized floors, smooth concrete walls. Decoration includes pictures of landscapes. It is equipped with state of the art exercise equipment.	The exercise environment is marked by years of use and resembles many existing exercise facilities at hospitals and rehabilitation clinics. It is located in the basement of an older campus building and has no windows. Access through a series of staircases and dark hall-ways. The room appears used with polished wooden floors, wall-bars, bare, unadorned concrete walls.
Year building completed	2012	1974
Picture		
Participant satisfaction (95% CI)		
Physical environment (p=0.00)	3.9 (3.6 to 4.1)	3.4 (3.2 to 3.6)
Exercise (p=0.45)	4.3 (4.1 to 4.5)	4.4 (4.2 to 4.7)
Interior		
Wall decorations (y/n)	y	n
Vista/windows (y/n)	y	n
Music during exercise (y/n)	y	y
Light (SD)		
Source	Daylight + artificial	Artificial
Strength (Lux)	2168 (744)	552 (39)
Air quality		
CO_2 (ppm)	Appendix	Appendix
Temperature (°C)	Appendix	Appendix
Humidity (%)	Appendix	Appendix
Sound/noise (SD)		
Background noise (dB(A))	31.8 (3.9)	41.2 (2.4)
Speech Clarity Index (C50)	1.8 (1.3)	0.7 (0.8)
Speech Transmission Index (STI)	0.7 (0.0)	0.6 (0.0)
Reverberation (T20)	0.92	0.95
Interpretation from acoustician	Generally, all four acoustic measurements favor the EX+ROOM environment over the EX environment, the differences were small. Regarding reverberation, the EX environment has higher numbers in the low frequency area, which will be perceived as echoing in the room.	

Table 1: Satisfaction with room is a total score compiled from 9 single items. Satisfaction with exercise is a total score compiled from 2 single items. Satisfaction scores range from 0-5. Mean with 95% Confidence intervals are

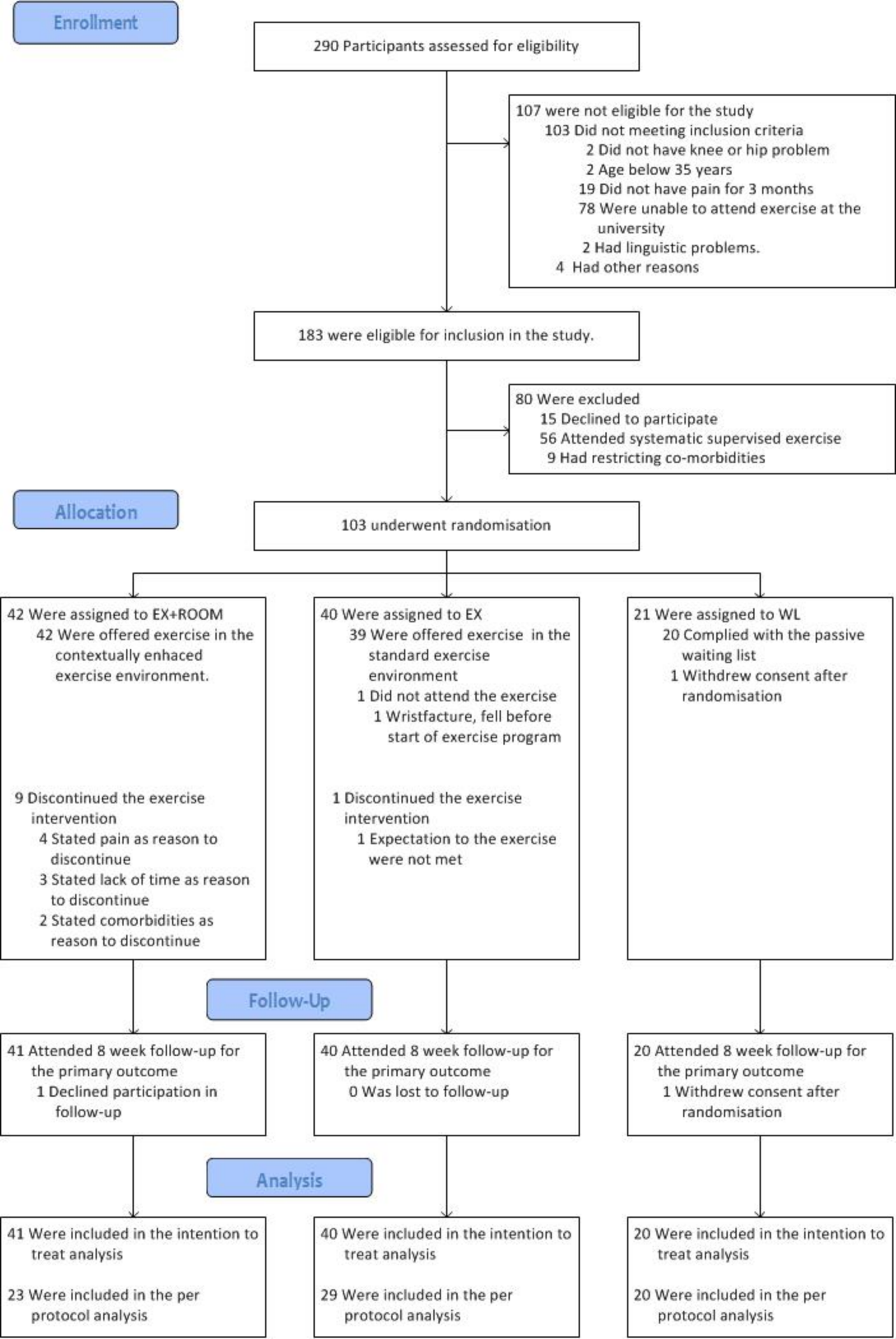
presented. Ppm: parts per million, C50, clarity index with first 50 msec of sound (mean across frequencies from 250Hz to 8kHz), STI: speech interpretability index, T20: reverberation time for sound decay of 20 dB (from 400Hz-1,25kHz). SD; Standard Deviation. All acoustic measurements are available on request to the author.

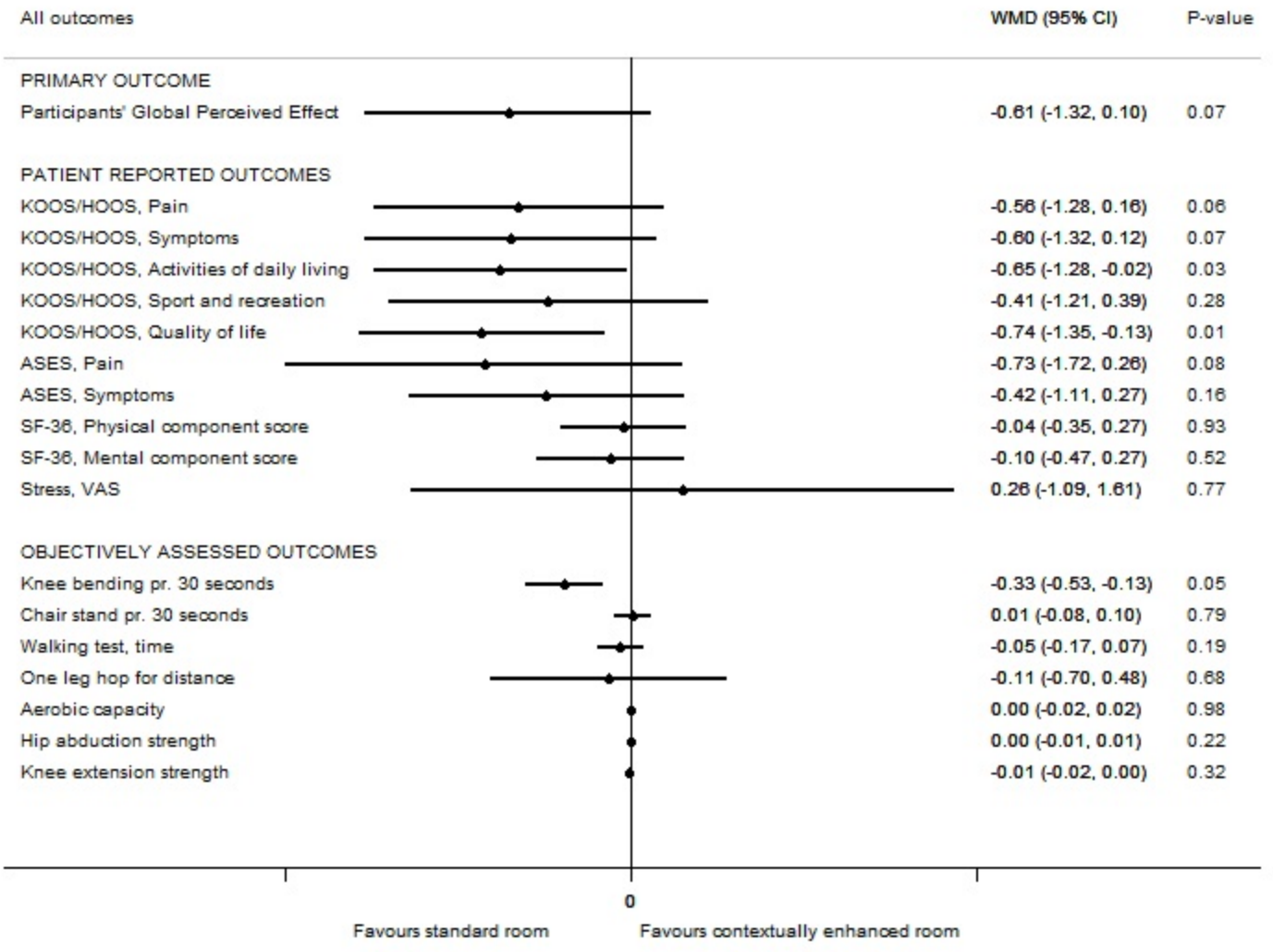
1

Table 2: Baseline characteristics for participants	Contextually enhanced environment n=42	Standard environment n=40	Waitlist n=21	p-value
Women, n, (%)	25 (60%)	25 (63%)	13 (62%)	0.96
Age (years), mean (SD)	59.6 (10.9)	57.6 (9.8)	58.2 (7.9)	0.65
BMI, mean (SD)	28.4 (5.0)	28.0 (5.8)	29.1 (7.0)	0.79
Medical comorbidities, participant median pr. group, n,	2	1	2	0.276
Index joint, knee (%)	26 (62%)	26 (65%)	13 (62%)	0.95
Clinical OA diagnosis, n, (%)	22 (52%)	26 (65%)	13 (62%)	0.48
Pain index joint, NRS, mean (SD)	3.9 (2.0)	3.6 (2.2)	4.1 (2.4)	0.57
Pain duration, n, (%)				0.61
0-6 months	1 (2%)	3 (7.5%)	0 (0%)	
6-12 months	4 (10%)	3 (7.5%)	1 (5%)	
1-5 years	20 (48%)	14 (35%)	11 (52%)	
< 5 years	17 (40%)	20 (50%)	9 (43%)	
Physical activity level, n, (%)				
Work				0.35
Very light	12 (29%)	9 (23%)	10 (48%)	
Light	11 (26%)	8 (20%)	5 (24%)	
Moderate	11 (26%)	18 (45%)	4 (19%)	
Strenuous	2 (5%)	2 (5%)	0 (0%)	
Unemployed	6 (14%)	3 (7%)	2 (9%)	
Leisure				0.12
Very light	4 (9%)	1 (3%)	0 (0%)	
Light	5 (12%)	9 (22%)	6 (29%)	
Moderate	18 (43%)	16 (40%)	5 (24%)	
Active	10 (24%)	14 (35%)	8 (38%)	
Very Active	5 (12%)	0 (0%)	2 (9%)	

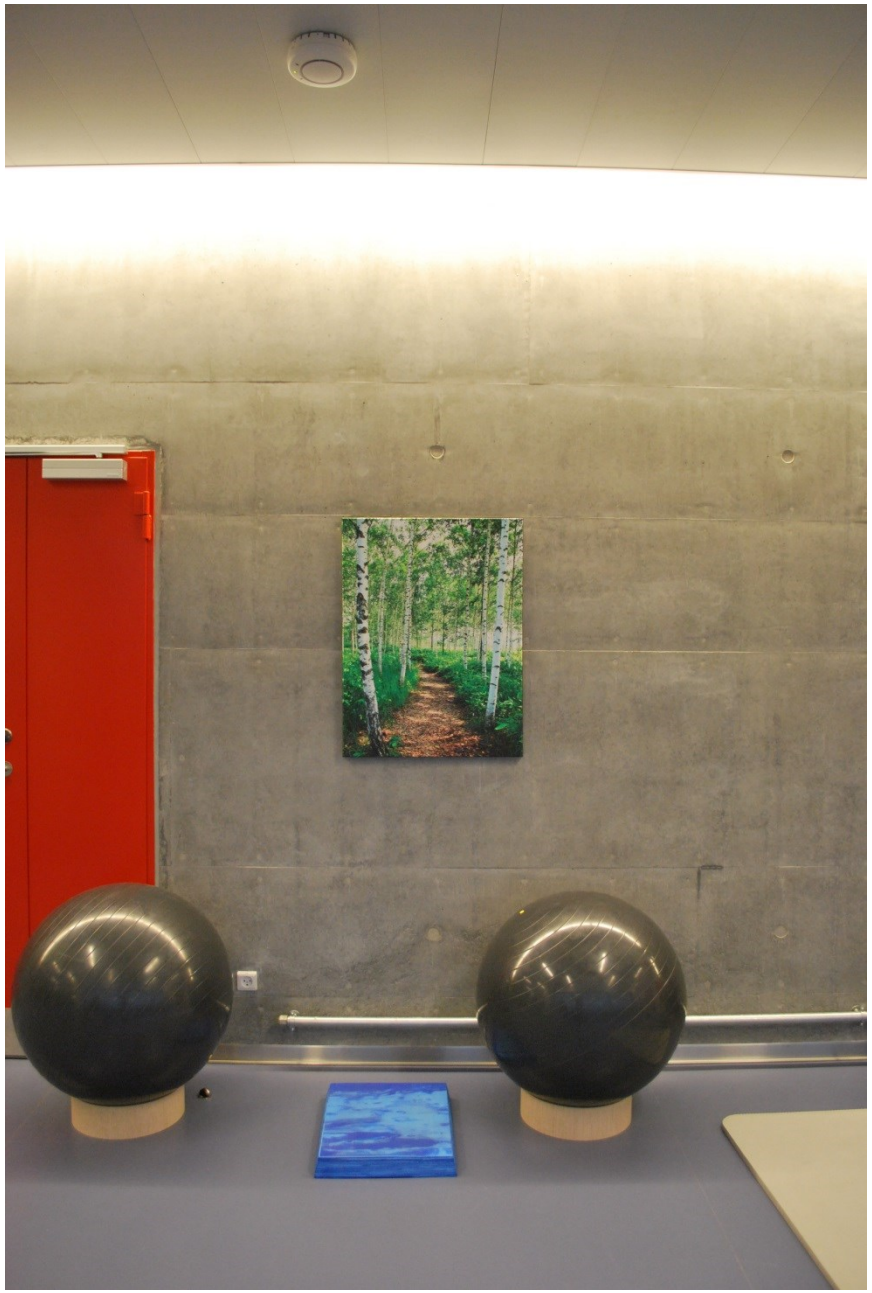
Table 2: SD, Standard Deviation, BMI, Body Mass Index, OA, osteoarthritis, NRS, Numerical Rating scale ranging from 0 - 10. Medical comorbidities are given as participants median for the group, comorbidities include heart disease, elevated blood pressure, lung disease, diabetes, ulcer, kidney or liver disease, anaemia, cancer, depression, arthritis, lower back problems, rheumatic disease or other self-reported medical comorbidities

2

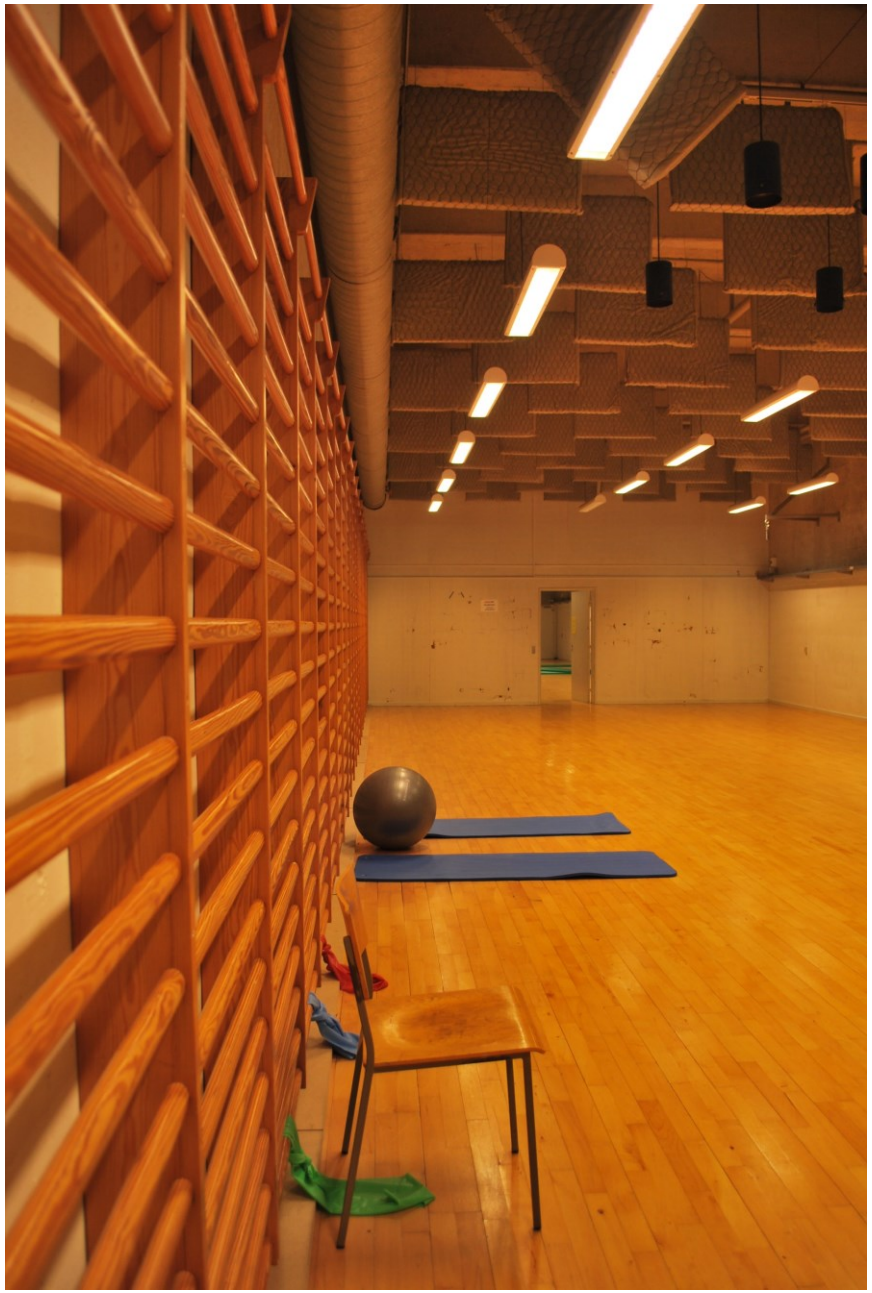

Enrollment
290 Participants assessed for eligibility
107 were not eligible for the study
103 Did not meeting inclusion criteria
2 Did not have knee or hip problem
2 Age below 35 years
19 Did not have pain for 3 months
78 Were unable to attend exercise at the university
2 Had linguistic problems.
4 Had other reasons
183 were eligible for inclusion in the study.
80 Were excluded
15 Declined to participate
56 Attended systematic supervised exercise
9 Had restricting co-morbidities
Allocation
103 underwent randomisation
42 Were assigned to EX+ROOM
42 Were offered exercise in the contextually enhaced exercise environment.
9 Discontinued the exercise intervention
4 Stated pain as reason to discontinue
3 Stated lack of time as reason to discontinue
2 Stated comorbidities as reason to discontinue
40 Were assigned to EX
39 Were offered exercise in the standard exercise environment
1 Did not attend the exercise
1 Wristfacture, fell before start of exercise program
1 Discontinued the exercise intervention
1 Expectation to the exercise were not met
21 Were assigned to WL
20 Complied with the passive waiting list
1 Withdrew consent after randomisation
Follow-Up
41 Attended 8 week follow-up for the primary outcome
1 Declined participation in follow-up
40 Attended 8 week follow-up for the primary outcome
0 Was lost to follow-up
20 Attended 8 week follow-up for the primary outcome
1 Withdrew consent after randomisation
Analysis
41 Were included in the intention to treat analysis
23 Were included in the per protocol analysis
40 Were included in the intention to treat analysis
29 Were included in the per protocol analysis
20 Were included in the intention to treat analysis
20 Were included in the per protocol analysis


All outcomes
WMD (95% CI)
P-value
PRIMARY OUTCOME
Participants' Global Perceived Effect
-0.61 (-1.32, 0.10)
0.07
PATIENT REPORTED OUTCOMES
KOOS/HOOS, Pain
-0.56 (-1.28, 0.16)
0.06
KOOS/HOOS, Symptoms
-0.60 (-1.32, 0.12)
0.07
KOOS/HOOS, Activities of daily living
-0.65 (-1.28, -0.02)
0.03
KOOS/HOOS, Sport and recreation
-0.41 (-1.21, 0.39)
0.28
KOOS/HOOS, Quality of life
-0.74 (-1.35, -0.13)
0.01
ASES, Pain
-0.73 (-1.72, 0.26)
0.08
ASES, Symptoms
-0.42 (-1.11, 0.27)
0.16
SF-36, Physical component score
-0.04 (-0.35, 0.27)
0.93
SF-36, Mental component score
-0.10 (-0.47, 0.27)
0.52
Stress, VAS
0.26 (-1.09, 1.61)
0.77
OBJECTIVELY ASSESSED OUTCOMES
Knee bending pr. 30 seconds
-0.33 (-0.53, -0.13)
0.05
Chair stand pr. 30 seconds
0.01 (-0.08, 0.10)
0.79
Walking test, time
-0.05 (-0.17, 0.07)
0.19
One leg hop for distance
-0.11 (-0.70, 0.48)
0.68
Aerobic capacity
0.00 (-0.02, 0.02)
0.98
Hip abduction strength
0.00 (-0.01, 0.01)
0.22
Knee extension strength
-0.01 (-0.02, 0.00)
0.32
0
Favours standard room
Favours contextually enhanced room

eMethods: Pictures of the contextually enhanced environment

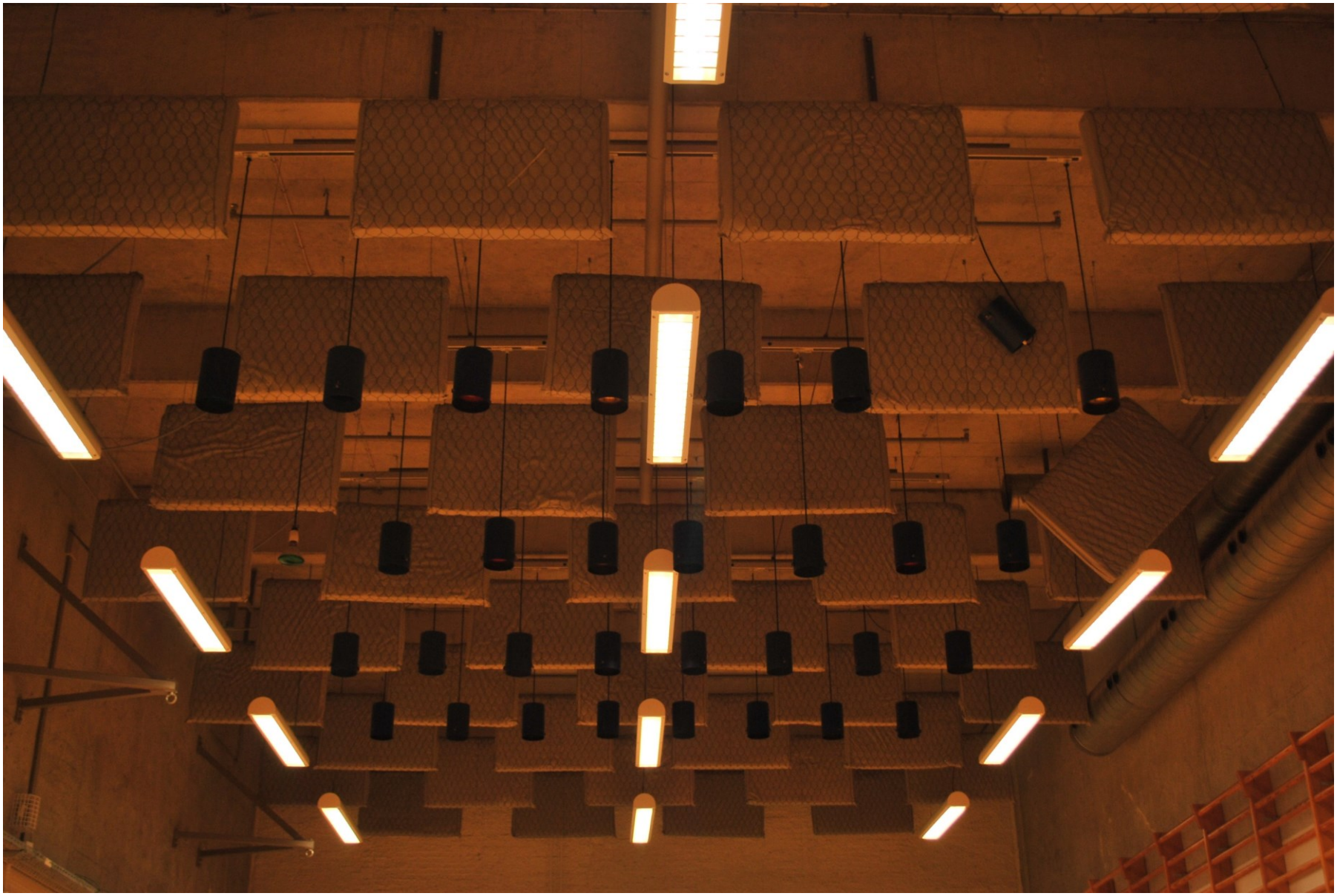


eMethods: Pictures of the standard environment




INGEN SKO
PÅ MÅTTEN!
SALEN BRUGES TIL
UNDERVISNING
TAG HENSYN
RYD OP!
Reebok
Reebok


KETTLER
KETTLER




SPRINKLER
17 CENTRAL 15

eTable1

eTable 1	Baseline, mean (95% CI)			Change score from baseline to 8 weeks follow-up (95% CI)			Group difference EX+ROOM vs. EX	
	1, EX+ROOM	3, EX	2, WL	EX+ROOM	EX	WL	mixed model*	p-value
KOOS (n=65)	(n=26)	(n=26)	(n=13)	(n=26)	(n=26)	(n=13)		
Pain	54.6 (48.3 to 60.9)	59.6 (54.0 to 65.2)	59.4 (49.6 to 69.2)	6.0 (-2.0 to 13.9)	8.9 (3.9 to 13.9)	-0.0 (-6.6 to 6.6)	2.9 (-4.9 to 10.7)	0.47
Symptoms	60.3 (54.3 to 66.3)	65.4 (59.1 to 71.7)	63.7 (54.2 to 73.3)	2.9 (-3.9 to 9.6)	4.0 (-1.1 to 9.1)	-0.3 (-7.2 to 6.6)	1.1 (-6.3 to 8.5)	0.77
ADL	59.2 (53.1 to 65.2)	64.0 (57.6 to 70.3)	66.2 (55.7 to 76.7)	7.0 (0.2 to 13.8)	11.0 (6.1 to 15.9)	2.6 (-3.4 to 8.6)	4.0 (-3.5 to 11.5)	0.29
Sport/Rec	29.0 (20.7 to 37.4)	31.0 (23.8 to 38.1)	32.7 (19.0 to 46.4)	10.8 (1.8 to 19.7)	13.3 (6.9 to 19.7)	2.7 (-9.8 to 15.2)	2.5 (-7.4 to 12.4)	0.62
QOL	37.5 (31.5 to 43.5)	36.1 (31.1 to 41.0)	39.4 (31.1 to 47.7)	4.5 (-2.0 to 11.0)	10.8 (5.9 to 15.7)	4.8 (-5.6 to 15.2)	6.4 (-0.3 to 13.0)	0.06
HOOS (n=38)	(n=16)	(n=14)	(n=8)	(n=14)	(n=14)	(n=7)		
Pain	59.7 (48.5 to 70.9)	58.0 (49.8 to 66.3)	63.1 (53.4 to 72.8)	2.3 (-5.9 to 10.6)	13.0 (4.7 to 21.4)	0.0 (-6.1 to 6.1)	10.6 (2.0 to 19.2)	0.02
Symptoms	56.3 (44.5 to 68.0)	55.0 (43.8 to 66.2)	63.1 (45.8 to 80.5)	-1.1 (-8.8 to 6.7)	13.9 (3.0 to 24.9)	-8.6 (-17.9 to 0.8)	14.3 (3.2 to 25.4)	0.01
ADL	67.1 (55.0 to 79.2)	67.3 (58.3 to 76.4)	66.4 (51.1 to 81.6)	3.8 (-3.3 to 10.9)	14.8 (8.5 to 21.1)	3.6 (-6.1 to 13.2)	10.9 (3.3 to 18.6)	0.01
Sport/Rec	53.1 (39.0 to 67.2)	51.8 (38.7 to 64.8)	57.8 (38.4 to 77.2)	4.9 (-3.6 to 13.5)	12.1 (5.6 to 18.5)	-4.5 (-11.6 to 2.7)	6.7 (-3.1 to 16.5)	0.18
QOL	46.5 (36.5 to 56.4)	42.4 (36.3 to 48.5)	44.5 (31.5 to 57.5)	4.5 (-2.8 to 11.7)	13.8 (7.7 to 20.0)	0.9 (-4.2 to 6.0)	8.7 (0.8 to 16.6)	0.03
KOOS/HOOS (n=103)	(n=42)	(n=40)	(n=21)	(n=40)	(n=40)	(n=20)		
Pain	56.5 (50.9 to 62.2)	59.1 (54.5 to 63.6)	60.8 (53.9 to 67.7)	4.7 (-1.1 to 10.5)	10.3 (6.0 to 14.6)	-0.0 (-4.7 to 4.7)	5.6 (-0.3 to 11.5)	0.06
Symptoms	58.8 (53.1 to 64.4)	61.8 (56.0 to 67.5)	63.5 (55.0 to 72.0)	1.5 (-3.6 to 6.6)	7.5 (2.3 to 12.6)	-3.2 (-8.8 to 2.5)	5.7 (-0.6 to 12.0)	0.08
ADL	62.2 (56.4 to 68.1)	65.2 (60.1 to 70.2)	66.3 (57.9 to 74.6)	5.9 (0.9 to 10.9)	12.4 (8.5 to 16.2)	2.9 (-2.0 to 7.9)	6.4 (0.8 to 12.1)	0.03
Sport/Rec	38.2 (30.1 to 46.3)	38.3 (31.2 to 45.3)	42.3 (30.2 to 54.4)	8.7 (2.3 to 15.2)	12.8 (8.2 to 17.5)	0.2 (-8.3 to 8.6)	4.1 (-3.3 to 11.4)	0.28
QOL	40.9 (35.6 to 46.3)	38.3 (34.4 to 42.2)	41.4 (34.5 to 48.3)	4.5 (-0.3 to 9.3)	11.9 (8.1 to 15.6)	3.4 (-3.4 to 10.3)	7.3 (2.1 to 12.4)	0.01

eTable 1, continued	Baseline, mean (95% CI)			Change score from baseline to 8 weeks follow-up (95% CI)			Group difference EX+ROOM vs. EX	
	1, EX+ROOM	3, EX	2, WL	EX+ROOM	EX	WL	mixed model	p-value
SF-36	(n=42)	(n=40)	(n=21)	(n=40)	(n=40)	(n=20)		
Physical component	38.4 (35.9 to 40.9)	40.5 (38.0 to 43.0)	39.6 (35.9 to 43.3)	3.2 (0.7 to 5.6)	3.6 (1.5 to 5.4)	0.7 (-1.7 to 3.0)	0.1 (-2.8 to 3.0)	0.93
Mental component	52.9 (49.7 to 56.2)	54.6 (51.4 to 57.7)	55.8 (53.5 to 58.2)	1.8 (-1.0 to 4.5)	2.8 (0.3 to 5.3)	-0.8 (-4.0 to 2.4)	1.1 (-2.3 to 4.5)	0.52
Arthritis Self-Efficacy Scale	(n=42)	(n=40)	(n=21)	(n=40)	(n=40)	(n=20)		
Pain	54.9 (49.3 to 60.4)	59.8 (53.6 to 65.9)	57.8 (48.6 to 67.0)	0.5 (-6.5 to 7.5)	7.8 (0.8 to 14.8)	3.6 (-4.3 to 11.5)	7.2 (-0.8 to 15.2)	0.08
Symptom	61.7 (56.2 to 67.2)	66.1 (61.9 to 70.3)	65.3 (58.5 to 72.7)	4.9 (-0.4 to 10.2)	9.1 (4.8 to 13.5)	1.8 (-3.7 to 7.4)	4.4 (-1.8 to 10.6)	0.16
Stress	(n=42)	(n=40)	(n=21)	(n=36)	(n=38)	(n=20)		
Stress, VAS 100 mm	34.0 (25.4 to 42.6)	31.1 (23.2 to 39.0)	22.1 (12.4 to 31.8)	-9.8 (-21.0 to 1.4)	-7.2 (-14.7 to 0.4)	-2.9 (-14.8 to 9.0)	1.9 (-10.9 to 14.7)	0.77
Physical performance tests	(n=42)	(n=40)	(n=21)	(n=34-35)	(n=36-38)	(n=19-20)		
Single-limb mini squat (over)	22 (54%)	19 (49%)	11 (52%)	23 (66%)	24 (667%)	18 (90%)	-0.5 (-2.3 to 1.3)	0.59
Knee bends/30 sec. (no.)	20.6 (17.3 to 23.9)	17.3 (15.1 to 19.5)	19.9 (15.7 to 24.0)	-0.1 (-2.6 to 2.4)	3.2 (1.3 to 5.2)	2.8 (0.3 to 5.2)	3.1 (0.0 to 6.2)	0.05
Chair stands/30 sec. (no.)	10.1 (9.2 to 11.0)	9.8 (9.0 to 10.5)	9.7 (8.4 to 11.0)	0.8 (0.1 to 1.5)	0.7 (0.3 to 1.2)	1.0 (0.4 to 1.6)	-0.1 (-0.9 to 0.7)	0.79
Walking test, 40 m (sec)	23.9 (22.5 to 25.2)	23.5 (22.0 to 25.1)	23.8 (21.6 to 25.9)	-0.1 (-0.9 to 0.7)	-0.6 (-1.5 to 0.2)	-0.8 (-1.6 to -0.1)	-0.7 (-1.8 to 0.3)	0.19
One-leg hop of distance (cm)	32.4 (22.8 to 42.1)	38.4 (29.0 to 47.8)	37.1 (24.3 to 49.9)	4.2 (-0.2 to 8.7)	5.3 (1.5 to 9.2)	4.1 (-2.3 to 10.4)	1.2 (-4.5 to 6.9)	0.68
Aerobic capacity (ml O_2/min/kg)	2.3 (1.2 to 3.9)	2.4 (0.2 to 3.7)	2.2 (1.1 to 3.8)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)	0.0 (-0.2 to 0.2)	0.98
Hip abduction (Nm*kg-1)	0.9 (0.8 to 1.1)	0.9 (0.8 to 1.0)	0.9 (0.7 to 1.1)	0.1 (-0.0 to 0.1)	0.1 (0.1 to 0.2)	-0.0 (-0.1 to 0.1)	0.1 (-0.0 to 0.2)	0.22
Knee extension (Nm*kg-1)	1.3 (1.1 to 1.4)	1.3 (1.1 to 1.4)	1.2 (1.0 to 1.5)	0.0 (-0.0 to 0.1)	0.1 (-0.0 to 0.2)	0.0 (-0.1 to 0.1)	0.1 (-0.1 to 0.2)	0.32

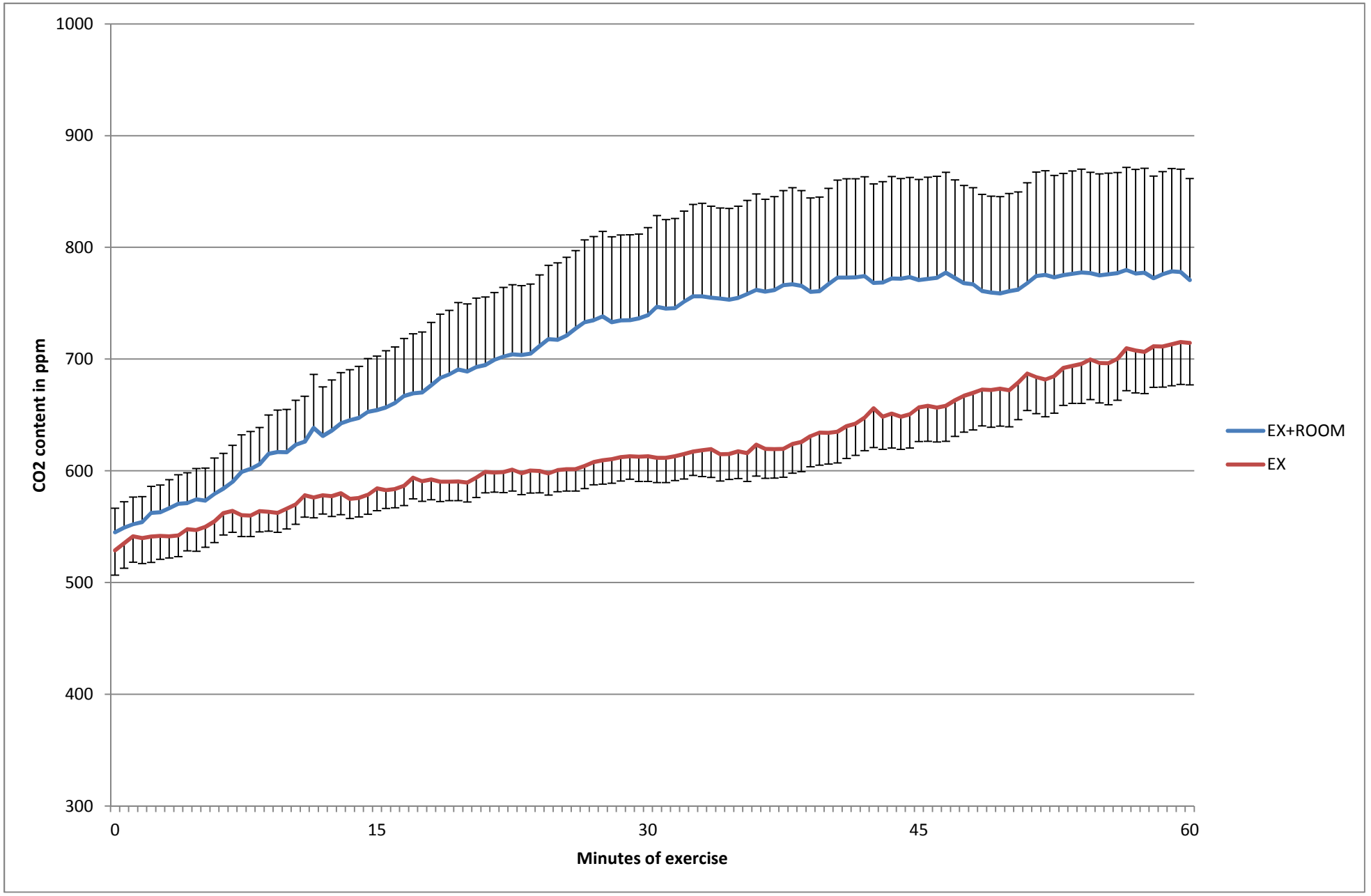
EX+ROOM: Contextually enhanced environemtn, EX: standard environment, WL: waitlist, KOOS, Knee injury and Osteoarthritis Outcomes Score, HOOS, Hip disability and Osteoarthritis Outcome Score, ADL, Activities of Daily Living, Sport/Rec, Sport and Recreational functions, QOL, Quality of Life. SD, Standard Deviation, CI, Confidence Intervals *Mixed linear model with time and group as fixed effect and participants as random effect (Single limb mini squat is binary outcome and therefore a mixed effect logistic regression was performed)

eTable2

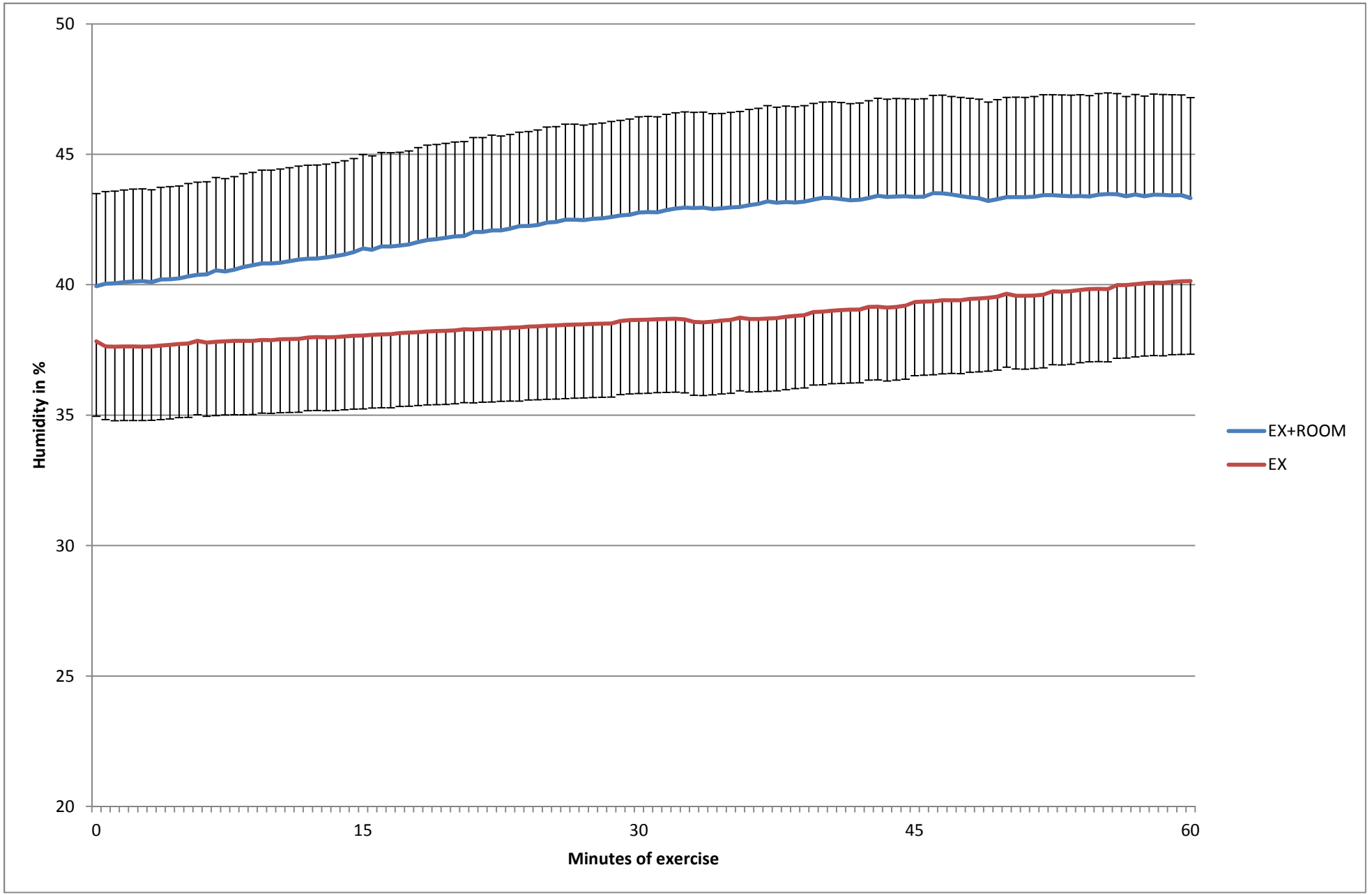
eTable 2: Self-reported adverse events, no of participants. (%)	EX+ROOM	EX	WL
Physical			
Increased pain at exercise	11 (26%)	7 (18%)	
Pain after baseline testing.	1 (2%)	0 (0%)	1 (5%)
Muscle soreness	1 (2%)	1 (3%)	
Muscle sprain	1 (2%)	1 (3%)	
Knee lock/pop	0 (0%)	2 (5%)	
Swelling	0 (0%)	1 (3%)	1 (5%)
Ligament injury	1 (2%)	0 (0%)	
pain, upper body	3 (7%)	3 (8%)	
Mental			
Exhaustion	2 (5%)	0 (0%)	
Bad mood	1 (2%)	0 (0%)	1 (5%)
Contact with GP (increased pain)	4 (10%)	3 (8%)	2 (10%)

eTable2: EX+ROOM: contextually enhanced environment, EX: standard environment, WL: waitlist. GP: general practitioner.

eMethods: CO2 content during exercise, comparison between contextually enhanced environment (EX+ROOM) and standard environment (EX).



eMethods: Air humidity in percentages during exercise, comparison between the contextually enhanced environment (EX+ROOM) and standard environment (EX)



eMethods: Temperature in Celcius during exercise, comparison between contextually enhanced environment (EX+ROOM) and standard environment (EX).