Strength training in addition to neuromuscular exercise and education in individuals with knee osteoarthritis the effects on pain and sensitization

Mikal Holm, Pætur; Kjær Petersen, Kristian; Wernbom, Mathias; Schrøder, Henrik Morville; Arendt-Nielsen, Lars; Skou, Søren T.

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Abstract

Background

There is a lack of evidence of the relative effects of different exercise modes on pain sensitization and pain intensity in individuals with knee osteoarthritis (KOA).

Methods

Ninety individuals with radiographic and symptomatic KOA, ineligible for knee replacement surgery, were randomized to 12 weeks of twice-weekly strength training in addition to neuromuscular exercise and education (ST+NEMEX-EDU) or neuromuscular exercise and education alone (NEMEX-EDU). Outcomes were bilateral, lower-leg, cuff pressure pain- and tolerance thresholds (PPT, PTT), temporal summation (TS), conditioned pain modulation (CPM), self-reported knee pain intensity, and number of painful body sites.

Results

After 12 weeks of exercise, we found significant differences in increases in PPT (-5.01 kPa (-8.29 to -1.73, p=0.0028)) and PTT (-8.02 kPa (-12.22 to -3.82, p=0.0002)) in the KOA leg in favor of ST+NEMEX-EDU. We found no difference in effects between groups on TS, CPM or number of painful body sites. In contrast, there were significantly greater pain-relieving effects on VAS mean knee pain during the last week (-8.4 mm (-16.2 to -0.5, p=0.0364) and during function (-16.0 mm (-24.8 to -7.3, p=0.0004)) in favor of NEMEX-EDU after 12 weeks of exercise.

Conclusion

Additional strength training reduced pain sensitization compared to neuromuscular exercise and education alone, but also attenuated the reduction in pain intensity compared to neuromuscular exercise and education alone. The study provides the first dose- and type-specific insight into the effects of a sustained exercise period on pain sensitization in KOA. Future studies are needed to elucidate the role of different exercise modes.

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Strength training in addition to neuromuscular exercise and education in individuals with knee osteoarthritis

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Pætur Mikal Holm[1,2], Kristian Kjær Petersen[3], Mathias Wernbom[4,5], Henrik Morville Schrøder[6,7], Lars Arendt-Nielsen[3], Søren T. Skou[1,2]

1. The Research Unit PROgrez, Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Region Zealand, Slagelse, Denmark
2. Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
3. Center for Neuroplasty and Pain, SMI, School of Medicine, Aalborg University, Aalborg Denmark.
4. Center for Health and Performance, Department of Food and Nutrition and Sport Science, University of Gothenburg, Gothenburg, Sweden
5. Department of Health and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
6. Department of Orthopedic Surgery, Næstved-Slagelse-Ringsted Hospitals, Næstved, Denmark
7. Department of Regional Health Research, University of Southern Denmark

Corresponding author: Pætur Mikal Holm (PT, PhD)

Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Fælledvej 2c, 4200 Slagelse, Region Zealand.

Phone: (+45) 61 14 48 33

Mail: pamh@regionsjaelland.dk / pholm@health.sdu.dk

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Conflicts of interest: STS is co-developer of the Good Life with osteoArthritis in Denmark (GLA:D) program, a not-for profit initiative to implement clinical guidelines in primary care. Furthermore, he is an Associate Editor of Journal of Orthopedic & Sports Physical Therapy and has received grants from The Lundbeck Foundation, personal fees from Munksgaard and TrustMe-ED, all of which are outside the submitted work.

Significance: This study is an important step towards better understanding the effects of exercise in pain management of chronic musculoskeletal conditions. We found that strength training in addition to neuromuscular exercise and education compared with neuromuscular exercise and education only had a differential impact on pain sensitization and pain intensity, but also that regardless of the exercise mode, the positive effects on pain sensitization and pain intensity were comparable to the effects of other therapeutic interventions for individuals with knee osteoarthritis.

Running head: Exercise and pain measures in knee osteoarthritis

Abstract

Background

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Methods

Ninety individuals with radiographic and symptomatic KOA, ineligible for knee replacement surgery, were randomized to 12 weeks of twice-weekly strength training in addition to neuromuscular exercise and education (ST+NEMEX-EDU) or neuromuscular exercise and education alone (NEMEX-EDU). Outcomes were bilateral, lower-leg, cuff pressure pain- and tolerance thresholds (PPT, PTT), temporal summation (TS), conditioned pain modulation (CPM), self-reported knee pain intensity, and number of painful body sites.

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Conclusion

Additional strength training reduced pain sensitization compared to neuromuscular exercise and education alone, but also attenuated the reduction in pain intensity compared to neuromuscular exercise and education alone. The study provides the first dose- and type-specific insight into the effects of a sustained exercise period on pain sensitization in KOA. Future studies are needed to elucidate the role of different exercise modes.

Introduction

Knee osteoarthritis (KOA) is a common and disabling condition, particularly in the elderly population with a rising global prevalence partly due to the combined effects of ageing, lifestyle changes and number of joint injuries (GBD 2019 Diseases and Injuries Collaborators, 2020; Hunter and Bierma-Zeinstra, 2019). Pain is the hallmark symptom in KOA (Neogi, 2013) and multiple studies have found localized and widespread hyperalgesia in individuals with KOA compared to non-KOA populations (Arendt-Nielsen et al., 2015a, 2015b; Lluch et al., 2014). Widespread hyperalgesia is most likely a component of generalized sensitization and is believed to be regulated in part by the impacted descending pain inhibition (Arendt-Nielsen et al., 2015b) and described to be impaired in severe chronic pain conditions(Arendt-Nielsen et al., 2018a) including KOA (Arendt-Nielsen et al., 2015a). Temporal summation of pain (TS) is often facilitated in severe KOA (Arendt-Nielsen et al., 2010, 2015a; Suokas et al., 2012) and is considered to reflect the process of wind-up in dorsal horn neurons as observed in animals (Arendt-Nielsen and Graven-Nielsen, 2011). Recent evidence suggests that individuals with KOA and generalized sensitization might be more susceptible to worse outcomes (i.e. more pain) following joint replacement surgery (Arendt-Nielsen et al., 2018b; Baert et al., 2016; Petersen et al., 2016), treatment with non-steroidal anti-inflammatory drugs (Arendt-Nielsen et al., 2016; Edwards et al., 2016; Petersen et al., 2019a, 2019b) and exercise therapy (Hansen et al., 2020; O'Leary et al., 2018), indicating that individuals with KOA and pain sensitization might respond less well to standard OA treatment.

Based on high-quality evidence, exercise is considered core first-line management of KOA along with weight loss and disease-specific education (Bannuru et al., 2019; Nelson et al., 2014) and there is evidence of hypoalgesic effects of exercise following acute bouts of exercise as well as longer-term (3 months) exercise programs in individuals with KOA (Burrows et al., 2014; Henriksen et al., 2014; Skou et al., 2016). Several mechanisms may cause the pain-relieving effects of exercise, such as central gating mechanisms (i.e. opioidergic, serotonergic, noradrenergic, and adrenergic pathways (Da Silva Santos and Galdino, 2018)), neuroimmune mechanisms (regulation of pro-inflammatory and anti-inflammatory cytokines (Leung et al., 2016)), and peripheral mechanisms (regulation of adipokines in plasma and cell proliferation and increased cell density locally at sites with tissue damage (Luan et al., 2015; Sun et al., 2019))(Lesnak and Sluka, 2020). Currently, it is unclear how different exercise modes may modulate pain in KOA differently due to a lack of high-quality randomized controlled trials investigating the longer-term (3 months) pain relieving effects of different exercise modes. Lower limb muscle strength, and especially knee extensor muscle strength, has repeatedly been suggested to affect both pain and function in KOA (Culvenor et al., 2017; Øiestad et al., 2015; Ruhdorfer et al., 2014; Sanchez-Ramirez et al., 2015). However, studies exploring the effects of strength training on measures of sensitization have mainly been restricted to laboratory-type investigations of responses to acute exercise bouts (within 20-30 min. of exercise cessation) and thus

provide little insight into effects from a sustained period of exercise while also not reflecting the current recommendations on the use of progressive strength training programs (Ratamess et al., 2009; Rice et al., 2019; Vaegter and Jones, 2020). This means that it remains to be seen whether exercise programs with a specific focus on strength training are superior to lower intensity, therapeutic exercise programs in eliciting a pain modulating response in individuals with KOA. A better understanding of the pain modulating response to different exercise modes will help optimize the non-surgical management of individuals with KOA.

Thus, the current pre-defined secondary analysis of a randomized controlled trial (RCT) aimed to investigate the effects of strength training in addition to neuromuscular exercise and education compared with neuromuscular exercise and education alone on experimental measures of pain sensitization and clinical measures of pain in individuals with KOA.

Methods

The current study is based on a secondary analysis from a patient-blinded, parallel-group RCT conforming to the CONSORT statement for reporting RCTs (Moher et al., 2010). The primary endpoint of the primary analysis was self-reported physical function after completing 12 weeks of exercise (Holm et al., 2020). Secondary endpoints were after 6 weeks of exercise and 12 months after completion of the exercise program (self-reported only). The 12-month follow-up will be reported independently at later time. The current secondary analysis reports the effects on experimental measures of pain sensitization as well as self-reported knee pain intensity and painful body sites after 6- and 12 weeks of exercise, pre-registered with the original registration at ClinicalTrials.gov (ID: NCT03215602).

Ethics

This study complied with the principles of the declaration of Helsinki and was approved by the Danish Scientific Ethical Committee, Region Zealand (SJ-517) as well as by the Danish Data Protection Agency (REG-61-2016). All patients provided written informed consent prior to baseline assessment and randomization.

Study population

From July 18, 2017 to October 3, 2018, we enrolled 90 individuals with symptomatic and radiographic KOA (Kellgren and Lawrence score ≥2) (Kellgren and Lawrence, 1957), deemed ineligible for knee replacement surgery by orthopedic surgeons in the orthopedic outpatient department at Næstved Hospital. The most prominent criteria for the decision on eligibility for surgery were radiographic severity, symptomatic severity and the individual's willingness to undergo surgery. For individuals who were ineligible for knee replacement surgery, further study-specific exclusion criteria were less than "mild" symptoms (score >75 in 0-100) on the subscale activities of

daily living from the Knee Injury and Osteoarthritis Outcome Score (KOOS-ADL) (Roos and Lohmander, 2003); morphine usage for pain other than knee joint pain; previous ipsilateral knee arthroplasty; rheumatoid arthritis; inability to comply with the protocol; and inadequacy in written and spoken Danish. Study staff approached relevant individuals at the outpatient department, informed them about the study and invited them to take part.

Randomization and allocation concealment

Patients were randomized (1:1 ratio) using permuted block randomization (blocks of 4 and 6). An external staff member administered the randomization list. Another external staff member put group allocation into sequentially numbered, sealed opaque envelopes, which the patients opened after baseline testing. The envelopes contained only the group allocation number without further details on the allocated exercise group.

Interventions

This study reported the exercise interventions in adherence to guidelines provided by the Consensus on Exercise Reporting Template (CERT), and recommended reporting of strength training interventions, provided by Toigo & Boutellier (see Appendix 1) (Slade et al., 2016; Toigo and Boutellier, 2006). The 12-week intervention was a group-based education and exercise sessions led by the same six physiotherapists throughout the study period. The physiotherapists were certified in the Good Life with osteoArthritis in Denmark (GLA:D®) program, which is the first-line non-surgical treatment for KOA in Denmark, that has also recently been implemented in Canada, Australia, China, Switzerland, New Zealand and Austria. GLA:D® consist of disease-specific education and neuromuscular exercise and education (Roos et al., 2018; Skou and Roos, 2017). All physiotherapists were also trained in the strength training protocol.

The training and education sessions took place at the exercise facilities in the Departments of Physiotherapy and Occupational Therapy at Næstved and Slagelse Hospitals, respectively. No home exercises were prescribed, and study participants were encouraged to carry on as normal with other daily-life activities outside the study interventions.

Education

Participants in both exercise arms received two educational sessions during the first week. The education was part of the GLA:D® education program and preceded each of the two exercise sessions during the first week. The first session consisted of osteoarthritis disease characteristics and symptoms, risk factors and introduction to treatment options. The second session focused on exercise as treatment, coping strategies and self-management (Skou and Roos, 2017).

Neuromuscular exercise

Both groups performed neuromuscular exercises twice weekly (60 min sessions) for 12 weeks (same as GLA:D® but 6 weeks longer). The neuromuscular exercises consisted of three parts; warm-up (≈10 min), circuit exercises (≈40 min) and cooldown/ stretching (≈10 min). The circuit exercises consisted of a total of 10 exercises, two for each domain of core stability, postural orientation, and functional exercises and four for leg muscle strength. All exercises were performed in 2-3 sets of 10-15 repetitions with three levels of difficulty (Ageberg et al., 2010). A complete description of the neuromuscular exercise set-up as well as further description of the GLA:D® program is provided elsewhere (Ageberg et al., 2010; Skou and Roos, 2017).

Strength training

The aim of the strength training protocol was to keep additional exercise time to a minimum to maintain clinical feasibility of the overall intervention, without substantially compromising potential clinical effects of the strength training program. Specifically, the aim of the additional strength training was to achieve high global activation of the quadriceps muscle through a combination of an open-kinetic-chain (OKC) exercise and a closed-kinetic-chain (CKC) exercise, using traditional knee extension and leg-press gym machines, respectively. Participants allocated to additional strength training performed one set of low-intensity, high-repetition (30-60RM) knee extensions followed by 4 sets of high-intensity (8-12RM) leg-press in gym machines. This was done approximately 10 min after cessation of the neuromuscular exercise session. The target of the low-intensity fatiguing set prior to high-intensity sets was to induce local muscular fatigue and thereby facilitate the recruitment of higher thresholds motor units in order to enhance gains in muscle mass and strength (Wernbom and Aagaard, 2020). A single, low-intensity, fatiguing strength training set prior to high-intensity strength training has previously been shown to enhance gains in muscle mass and strength compared to high intensity strength training alone in young men (Aguiar et al., 2015). The four sets of leg-press training with 8-12RM intensities is in line with recommendations by the American College of Sports Medicine (ACSM) regarding both intensity and volume of exercises to promote muscle hypertrophy (Ratamess et al., 2009). For a complete description of the strength training protocol, including load progression and pain monitoring strategies, please see Appendix 1. The group receiving strength training in addition to neuromuscular exercise and education is hereafter referred to as ST+NEMEX-EDU, whilst the group receiving neuromuscular exercise and education alone is termed NEMEX-EDU.

Outcomes

Participants were assessed at baseline prior to randomization and after 6 weeks of exercise (corresponding to the length of the GLA:D® program) and after completing 12 weeks of exercise in total. The same trained assessor performed all assessments, using a standardized test protocol at the department of Physiotherapy and Occupational Therapy, Slagelse Hospital. The pain pressure assessments reported in this study were performed as the final part of a larger test battery, which

contained performance-based and muscle function tests and lasted around 90 min. Self-reported knee pain intensity and painful body sites were reported as part of the follow-up online questionnaires at baseline, week 6 and week 12. Performance-based and muscle function results are reported in the primary report from the RCT (Holm et al., 2020).

Quantitative sensory testing of pain sensitization

The device consisted of a computer-controlled cuff algometer (Cortex Technology, Hadsund and Aalborg University, Aalborg, Denmark) including two 13-cm wide cuffs (VBM, Sulz, Germany) and an electronic Visual Analogue Scale (VAS) (Aalborg University, Aalborg, Denmark) (Petersen et al., 2019a). The computer continuously controlled the compression rate of the cuffs, measured in Kilopascal (kPa). The participants used the electronic VAS to rate the pain intensity to the different pressure stimuli patterns and a button to release the pressure for immediate termination of the cuff pressure. The electronic VAS was sampled at 10 Hz. The VAS pain scale ranged from zero (no pain) to 10 (worst imaginable pain). For safety, the inflation of the cuff could be terminated both mechanically and from the computer program in addition to the pressure release button at the electronic VAS, and the maximal pressure limit was set at 100 kPa.

The cuff assessments were performed with the participants sitting relaxed on a three-piece treatment bed using the elevated leg-section as backrest and a firm cushion under the knee. The computer monitor was turned away from the participant, ensuring that the participant could not see the display showing cuff pressure and pain ratings. Two cuffs were wrapped bilaterally around the lower legs. Both cuffs were placed with a finger-width distance between the upper rim of the cuff and the tibial tuberosity.

Participants received careful verbal introduction prior to each test. The full cuff assessment consisted of three sequences of pain-pressure measurements:

Cuff pressure pain and tolerance threshold

The assessment of cuff pressure pain thresholds (PPT) and tolerance thresholds (PTT) was performed on each leg separately, starting with the index leg or in case of bilateral KOA, the knee with most pain. During a slow increase in cuff pressure (1 kPa/s, i.e. 7.5 mm Hg/s), the participants were instructed to rate the pain intensity continuously on the electronic VAS and to press the pressure release button when the pain was intolerable. PPT was defined as the pressure in kPa where the VAS score exceeded 1 cm, as in previous KOA studies (Petersen et al., 2019a, 2019b). PTT was defined as the kPa pressure of the cuff when the participant pressed the stop button (Petersen et al., 2019a).

Temporal summation

Temporal summation (TS) was assessed by inflating the cuff on the index leg. The participant was subjected to ten short-lasting pressure stimuli (1-second each), using the previously recorded PTT cuff pressure, with 1-second breaks between each stimuli. The participants were instructed to rate the pain intensity immediately after the first stimulus and then continuously throughout the subsequent stimuli on the electronic VAS without returning the cursor to zero between each stimulus. The participants were kept unaware of the pressure being the same throughout all 10 stimuli. For analysis of TS, the mean VAS score was summarized for the first to the fourth stimulus and for the eighth to the tenth stimulus, respectively. The TS effect was defined as the mean VAS value of the eighth to the tenth stimulus subtracted by the mean VAS value of the first to the fourth stimulus and used for the between-group analysis (Petersen et al., 2017).

Conditioned Pain Modulation

For the assessment of conditioned pain modulation (CPM), both cuffs were inflated. The conditioning stimulus was applied contralaterally to the index leg as a constant stimulus using 70% of the recorded PTT for the contralateral leg from the previous assessment. The cuff on the index leg was inflated continuously with a rate of 1 kPa/s, similar to the initial PPT and PTT assessments. For this CPM assessment, the participants were instructed to only focus on the cuff pressure stimulus on the index leg and to disregard the conditioning pressure stimulus on the opposite leg when rating the VAS pain. The participants were instructed to press the pressure release button when the pain was intolerable. Conditioned PPT was defined as the pressure in kPa where the VAS score exceeded 1 cm. For analyzing purposes, the CPM effect was defined as the difference in kPa, when subtracting the conditioned PPT by the previously recorded PPT without conditioning stimuli on the KOA leg, as in previous KOA studies (Petersen et al., 2019b). The difference in PPT with and without conditioning stimuli was recorded for the between-group analysis.

Severity of knee pain and number of painful body sites

Knee pain intensity was assessed on a 100mm VAS scale with terminal descriptors of ‘no pain’ (0mm) and ‘worst pain imaginable’ (100mm) and patients rated their pain intensity for the following domains; 1. Mean knee pain intensity during the previous 24h; 2. Mean knee pain intensity during the last week; 3. Mean knee pain intensity following 30min. of walking. VAS is a simple, reliable, valid and responsive generic pain measure, applicable across a broad range of populations and settings (Hawker et al., 2011).

In the assessment of painful body sites, participants were asked to mark body sites with pain during the last week on a region-divided bodychart (21 sites in total). The mean number of painful body sites was derived and compared between groups (Coggon et al., 2013).

Blinding

By exercising on separate days, patients were kept unaware of the content of exercise in the comparator group and therefore did not know if they had been randomized to the intervention or comparator exercises. The assessor conducting the assessment was blinded to group allocation and the patients were carefully instructed not to reveal any details of the content of their exercise sessions to the assessor.

Sample size

The sample size was powered for the primary analysis of the RCT and was based on the recommended clinically important difference of 10 points on the KOOS questionnaire (Roos and Lohmander, 2003). With a common standard deviation (SD) of 15 and power of 80% ($\alpha = 0.05$ (two-sided)), 37 participants were required in each group to detect a 10-point between-group difference at 12-week follow-up (Roos and Lohmander, 2003). Based on previous studies, this was also deemed sufficient for the purpose of the current study (Henriksen et al., 2014; Tubach et al., 2005).

Statistical analysis

This secondary analysis was pre-specified and followed the same detailed statistical analysis plan as the primary analysis. The statistical analysis plan was made publicly available before analyses of the results began (see appendix 2). An independent statistician, unaware of group allocation performed all analyses (primary and secondary), following the Intention-To-Treat (ITT) principle and included all randomized participants in the analysis.

PPT, PTT, TS, CPM, VAS pain (24 hours, last week, after 30 min. walk), and painful body sites, were compared between groups using a mixed model repeated measurements (MMRM) analysis of variance with participants as a random factor and treatment (ST+NEMEX-EDU, NEMEX-EDU) and time (assessments at baseline, 6 and 12 weeks) as fixed factors. Baseline values were included as covariates in the analysis of change from baseline and treatment-by-time was included as interaction terms to assess the interaction between treatment allocation (ST+NEMEX-EDU or NEMEX-EDU) and time (follow-up at 6- and 12 weeks). The model was based on the assumption of a covariance structure with compound symmetry. Between-group differences at 6- and 12 weeks were reported using estimated marginal means and 95% CI with P values for superiority assessment.

All analyses were performed using STATA 15.1 (StataCorp, College Station, TX, USA).

Results

A total of 160 individuals with KOA, who were not eligible for knee replacement surgery, were assessed for eligibility to participate in this study. 104 were eligible for inclusion; 8 of these did not wish to participate after consideration, 2 chose other treatment options and 4 did not show up for baseline tests. A total of 90 individuals (see table 1 for baseline characteristics) were randomized and

35 (78%) in the ST+NEMEX-EDU group and 42 (93%) in the NEMEX-EDU group completed the 12-week follow-up. The cited reasons for not completing the intervention period and not completing follow-ups were; logistical (ST+NEMEX-EDU n=3, NEMEX-EDU n=1), knee replacement surgery (ST+NEMEX-EDU n=2), inability to comply with study protocol (ST+NEMEX-EDU n=2), unrelated health condition and hospitalization (ST+NEMEX-EDU n=1, NEMEX-EDU n=1) exacerbation of knee pain (NEMEX-EDU n=1), family reasons (ST+NEMEX-EDU n=1), unknown (ST+NEMEX-EDU n=1). Reasons for discontinuing were considered unrelated to treatment allocation. For further information on the study flow (including flow chart), please see the primary report of this study (Holm et al., 2020).

>>>>>>>>>>INSERT TABLE 1 HERE<<<<<<<<<<

Quantitative sensory testing of pain sensitization

For PPT in the KOA leg, there was a statistically significant difference between groups, with higher thresholds (less sensitization) in the ST+NEMEX-EDU group at week 6 (adjusted mean difference: -3.98 kPa (-7.12 to -0.84), p=0.013) and week 12 (adjusted mean difference: -5.01 kPa (-8.29 to -1.73), p=0.0028). For PTT in the KOA leg, there was a statistically significant difference between groups, with higher thresholds (less sensitization) in the ST+NEMEX-EDU group at week 6 (adjusted mean difference: -4.63 (-8.69 to -0.57), p=0.0255) and week 12 (adjusted mean difference: -8.02 kPa (-12.22 to -3.82), p=0.0002). There were no significant differences between groups in TS or CPM at 6 or 12 weeks. See table 2 and figure 1 for a complete presentation of results, including the contralateral leg.

>>>>>>>>>>INSERT TABLE 2 HERE<<<<<<<<<<

>>>>>>>>>>INSERT FIGURE 1 HERE<<<<<<<<<<

Knee pain intensity and number of painful body sites

There was a statistically significant difference between groups in VAS knee pain during the last week at week 12, with a larger pain reduction in the NEMEX-EDU group; adjusted mean difference of -8.4 (-16.2 to -0.5), p=0.0364. There was also a statistically significant difference between groups in VAS pain after 30 min. of walking at week 12, with a larger pain reduction in the NEMEX-EDU group; adjusted mean difference of -16.0 (-24.8 to -7.3), p=0.0004. There were no statistically significant differences between groups in knee pain intensity during the last 24h or in number of painful body sites at 6- or 12-weeks (see table 3 and figure 2).

Please see appendix 3 for within-group values (mean (SD)) of all outcomes at baseline, 6- and 12 weeks.

>>>>>>>>>>INSERT TABLE 3 HERE<<<<<<<<<<

>>>>>>>>>>INSERT FIGURE 2 HERE<<<<<<<<<<

Discussion

This is the first RCT comparing the effects of different exercise modes on pain sensitization and clinical pain scores in individuals with KOA, not eligible for knee replacement surgery. We found that strength training in addition to neuromuscular exercise and education reduced sensitization as assessed quantitatively by PPT and PTT compared to neuromuscular exercise and education alone. This indicated an additional effect of strength training on pain sensitization in individuals with KOA. In contrast, assessments of knee pain intensity showed that neuromuscular exercise and education alone had a greater pain-relieving effect compared to neuromuscular exercise and education with additional strength training. This, on the other hand, indicated an attenuating effect of additional strength training on clinical pain-relief over time.

Comparison of effects across exercise modes

Compared to low-intensity neuromuscular exercises, higher intensity strength training can be considered a more vigorous exercise form, inducing higher mechanical and metabolic stress on the exercising muscles (Folland and Williams, 2007; Kraemer and Ratamess, 2005). Studies have shown that acute bouts of exercise to muscular fatigue induces nociceptive activity (Taylor et al., 2000), which in turn may trigger the activation of endogenous descending inhibitory and facilitatory pathways from the brain (Villanueva et al., 1996). However, it is unclear whether longer-term (3 months) exposure to fatiguing muscle contractions and contractions to volitional muscle failure, as per the protocol in the current strength training group, triggers these same endogenous pathways and/or if these or other pathways are activated differently compared to other exercise modes (Lesnak and Sluka, 2020). This also means that we are unable to recognize which specific pathways that may account for the greater effects on pain sensitization from additional strength training. The same applies to the evidence of exercise-induced neuroimmune responses that interact with the nociceptive system (neutralization of pro-inflammatory cytokines) (Helmark I.C. et al., 2010; Leung et al., 2016; Nees et al., 2019; Watkins and Maier, 2005); despite suggestions that different cytokines are involved in different qualities of pain, such as mechanical or thermal pain (Schaible, 2014), there is currently no evidence linking different exercise modes to the neutralization of specific pro-inflammatory cytokines. Nevertheless, considering the contrasting directions of our findings on experimental pain (favoring additional strength training) and clinical pain (disfavoring additional strength training), the addition of strength training targeting muscle fatigue and volitional muscle failure had both beneficial and detrimental effects on pain measures. The mean difference in clinical pain during function at 12 week follow-up (16 mm on VAS 0-100), favoring NEMEX-EDU exceeds the proposed Minimal Important Difference (MID) of 15 mm for VAS pain measures in KOA (Tubach et al., 2005). This indicates that performing neuromuscular exercise and education only carried a clinically relevant

pain-relieving effect over the same exercise mode with additional strength training. This finding was not consistent with the primary analysis of this RCT, showing similar pain relief between groups at 12 weeks on other self-reported pain measures (Holm et al., 2020). Notably, when assessing effects on clinical pain over the different time points in this study, it seems that both exercise modes provided similar clinical pain relieving effects throughout the first 6 weeks of the intervention period. Thereafter, from 6 weeks to 12 weeks, the pain continued to decrease at a somewhat similar rate for NEMEX-EDU, but with a plateauing or even inverted tendency for ST-NEMEX-EDU (table 3, figure 2). A similar inverted tendency for longer periods of exercise has been found in rodent pain models (Cobianchi et al., 2010). A meta-analysis on exercise in KOA showed that exercise therapy programs with a single focus (i.e. neuromuscular exercises) were more efficacious in reducing pain than exercise therapy programs combining several exercise modes (i.e. neuromuscular exercises and strength training) (Juhl C. et al., 2014). However, there were large differences in the exercise program characteristics (large heterogeneity) and the proposed reason for the discrepancy among different exercise therapy programs (interfering molecular and myofibrillar protein responses) is a phenomenon which may occur when combing endurance training and strength training (Karavirta et al., 2011) and therefore arguably does not apply to this study. In a Cochrane review, which compared low-intensity exercise programs to high-intensity exercise programs, the authors were unable to determine the effects of different types of intensity on pain measures due to insufficient evidence (Regnaux J.-P. et al., 2015). Taken together, it is possible that the high-intensity strength training in addition to a one-hour session of neuromuscular exercise and education, meant that participants in the ST+NEMEX-EDU group reached a tipping point regarding the influence of the total volume of exercise on the effects on pain relief halfway through the intervention period. Although this is speculative, our results underscore the need for a better understanding of the dose-response curve of pain-relieving effects across the exercise intensity and volume continuum as well as the effects of different types of exercise.

Comparisons to other randomized controlled trials of therapeutic interventions

The direction of the effects across both exercise modes indicates overall positive effects of exercise on both measures of pain sensitization and clinical pain in individuals with KOA. The effects for PPT of the most affected leg (favoring ST+NEMEX-EDU) at 12 weeks corresponds to a between-group standardized mean difference (SMD) of 0.43, which is slightly lower than the SMD for PPT of 0.48 previously reported after 12 weeks of supervised exercise therapy (low-intensity stability, coordination and strength exercises) in KOA (Henriksen et al., 2014). Importantly, Henriksen and colleagues reported exercise effects compared to no attention control (Henriksen et al., 2014), whereas the current study investigated the effects of exercise in the context of two active treatment arms, providing a more robust and specific measure of effectiveness of different exercise modes. The effects for PPT in the current study are higher than the SMD of 0.30 for the effects of knee

replacement surgery in addition to non-surgical treatment including neuromuscular exercise and education compared to the same non-surgical treatment alone at one-year, using an aggregate PPT score from five sites (Arendt-Nielsen et al., 2018b). For clinical pain, the observed between-group effects on knee pain intensity during the last week and knee pain intensity during function (favoring NEMEX-EDU) corresponded to a SMD of 0.38 and 0.55, respectively. In comparison, Henriksen and colleagues (exercise compared to no attention control), found a similar effect on self-reported pain (SMD: 0.54) (Henriksen et al., 2014). For the effects of knee replacement surgery in addition to non-surgical treatment, Arendt-Nielsen and colleagues found a higher effect compared to non-surgical treatment alone, with a SMD of 0.65 (Arendt-Nielsen et al., 2018b). Taken together, this study showed that neuromuscular exercise and education with and without strength training for individuals with KOA, is a potent therapeutic intervention for improving pressure pain thresholds and clinical pain, with effect sizes in the proximity of other efficacious therapeutic interventions.

Limitations

This study has limitations. Firstly, the study sample was powered for the primary RCT. Due to this and to the explorative nature of the analyses, readers should interpret these findings with caution. Secondly, there are some uncertainties regarding reliability and measurement error of the cuff algometer in the assessment of pressure pain and tolerance thresholds (Graven-Nielsen et al., 2015; Imai et al., 2016), which means that we cannot rule out some degree of learning effects for this outcome. The fact that we did not include learning attempts during assessments is a limitation to the interpretation of this outcome. Additionally, we are unaware of established cut-offs for minimal detectable change (MDC) and MID in pain sensitization assessed by cuff pressure algometry. As such, we are unable to infer clinical relevance of the observed differences in PPT and PTT between the two exercise modes. The current study only applied deep pressure stimuli, which has consistently been utilized to assess individuals with OA (Izumi et al., 2017; Kurien et al., 2018; Petersen et al., 2017, 2019a, 2019b), but some studies find thermal changes in patients with OA (Izumi et al., 2017; King et al., 2013; Kuni et al., 2015; Moss et al., 2016) – this was not assessed in the current study and therefore limits the generalizability of our findings. Thirdly, only 19 participants (42%) in the group receiving additional strength training adhered to pre-determined frequencies and intensities (Holm et al., 2020). This is important to consider when interpreting the additional effects of strength training.

Conclusion

The addition of strength training to 12 weeks of twice-weekly neuromuscular exercises and education reduced pain sensitization more than neuromuscular exercise and education alone in individuals with KOA, not eligible for knee replacement surgery. In contrast, the addition of strength training seemed to attenuate the reductions in knee pain intensity over time compared to neuromuscular exercise and education alone at 12-week follow-up. This study was the first of its kind, providing dose- and type-

specific insights into the effects of a sustained period of exercise on pain sensitization in KOA. Future work needs to elucidate the roles and interplay between experimental pain and clinical pain and the possible association between these pain outcomes and different exercise modes.

Author contributions

Study conception and design: Holm, Wernbom, Schrøder, Skou

Recruitment of patients: Holm, Schrøder

Acquisition of data: Holm

Analysis and interpretation of data: Holm, Skou

Drafting the article or revising it critically for important intellectual content: Holm, Petersen, Wernbom, Schrøder, Arendt-Nielsen, Skou

Final approval of the article: Holm, Petersen, Wernbom, Schrøder, Arendt-Nielsen, Skou

All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

STS is co-developer of the Good Life with osteoArthritis in Denmark (GLA:D) program, a not-for profit initiative to implement clinical guidelines in primary care. Furthermore, he is an Associate Editor of Journal of Orthopedic & Sports Physical Therapy and has received grants from The Lundbeck Foundation, personal fees from Munksgaard and TrustMe-ED, all of which are outside the submitted work.

Tables and figures

Table 1 | Baseline characteristics of participants

Table legend:

[a]Measured on a visual analog scale (VAS) with terminal descriptors of 'no pain' (0mm) and 'worst pain imaginable' (100mm). [b]Number of painful body sites during the last week marked on a region-divided bodychart (21 sites). [c]Pain pressure threshold in kPa of the most affected leg. [d]Pain pressure threshold in kPa of the least affected leg. [e]Pain tolerance threshold in kPa of the most affected leg. [f]Pain tolerance threshold in kPa of the least affected leg. [g]Temporal summation of pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimuli. [h]The difference in pain pressure thresholds in kPa with and without condition stimuli.

[i]Strength training in addition to neuromuscular exercise and education.

[j]Neuromuscular exercise and education.

Table 2 | Quantitative sensory testing at 6- and 12 weeks

Table legend:

[a]Pain pressure threshold in kPa of the most affected leg. [b]Pain pressure threshold in kPa of the least affected leg. [c]Pain tolerance threshold in kPa of the most affected leg. [d]Pain tolerance threshold in kPa of the least affected leg. [e]Temporal summation of pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimuli. [f]The difference in pain pressure thresholds in kPa with and without condition stimuli.

[g]Strength training in addition to neuromuscular exercise and education.

[h]Neuromuscular exercise and education

[i]Adjusted for baseline imbalance.

[j]Analysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the analyses.

[k]$p < 0.05$.

Table 3 | Knee pain intensity and number of painful body sites at 6- and 12 weeks

Table legend:

[a]Measured on a visual analog scale (VAS) with terminal descriptors of 'no pain' (0mm) and 'worst pain imaginable' (100mm). [b]Number of painful body sites during the last week marked on a region-divided bodychart (21 sites).

[c]Strength training in addition to neuromuscular exercise and education.

[d]Neuromuscular exercise and education

[e]Adjusted for baseline imbalance.

[f]Analysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the analyses.

[g]$p < 0.05$.

Figure 1 | Quantitative sensory testing of the most symptomatic leg

Figure legend:

a) Change in pain pressure thresholds (kPa) on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).
b) Change in pain tolerance thresholds (kPa) on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).
c) Change in temporal summation of pain, defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimul on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).
d) Change in the difference between pain pressure thresholds (kPa) with and without conditioning stimuli on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).

Figure 2 | Knee pain intensity and number of painful body sites

Figure legend:

a) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past 24 hours on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)
b) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past week on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)
c) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) after 30 min walking on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the

two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)

d) Change in the number of painful body sites during the last week marked on a region-divided bodychart (21 sites) from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)

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Table 1 | Baseline characteristics of participants

	ST+NEMEX-EDU[i]	NEMEX-EDU[j]
Sex, females (n (%))	25 (56)	27 (60)
Age, years (mean (SD))	63.2 (10.7)	66.4 (9.3)
Body mass index (mean (SD))	32.2 (6.5)	29.6 (5.4)
Location and severity of knee pain		
Study knee, right (n (%))	18 (40)	18 (40)
Bilateral pain (n (%))	31 (69)	28 (62)
Pain past 24 hours, 0-100[a] (mean (SD))	52 (22)	48 (20)
Pain past week, 0-100[a] (mean (SD))	55 (21)	51 (18)
Pain after 30 min. walking[a], 0-100 (mean (SD))	58 (25)	54 (26)
Body sites with pain[b], (mean (SD))	4.7 (3.2)	4.6 (2.7)
Quantitative sensory testing		
PPT, KOA leg[c] (mean (SD))	22.1 (7.9)	20.4 (9.7)
PPT, contralateral leg[d] (mean (SD))	22.9 (11.5)	19.3 (8.5)
PTT, KOA leg[e] (mean (SD))	45.5 (17.1)	46.8 (17)
PTT, contralateral leg[f] (mean (SD))	46.9 (20.1)	44.1 (15.7)
TS, KOA leg[g] (mean (SD))	1.9 (1.4)	2.3 (1.5)
CPM, KOA leg[h] (mean (SD))	1.2 (10.3)	2.3 (9.3)

[a]Measured on a visual analog scale (VAS) with terminal descriptors of 'no pain' (0mm) and 'worst pain imaginable' (100mm). [b]Number of painful body sites during the last week marked on a region-divided bodychart (21 sites). [c]Pain pressure threshold in kPa of the most affected leg. [d]Pain pressure threshold in kPa of the least affected leg. [e]Pain tolerance threshold in kPa of the most affected leg. [f]Pain tolerance threshold in kPa of the least affected leg. [g]Temporal summation of pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimuli. [h]The difference in pain pressure thresholds in kPa with and without condition stimuli.

Table 2 | Quantitative sensory testing at 6- and 12 weeks

Estimated marginal means (95%CI)				
	ST+NEMEX-EDU[g] (n=90)[j]	NEMEX-EDU[h] (n=90)[j]	Adjusted between-group difference[i]	p
PPT, KOA leg[a]				
6 weeks	23.7 (21.4 to 26.0)	19.7 (17.6 to	-3.98 (-7.12 to -0.84)	0.013[k]
12 weeks	24.6 (22.1 to 27.1)	19.6 (17.4 to	-5.01 (-8.29 to -1.73)	0.0028[k]
PPT, contralateral leg[b]				
6 weeks	24.7 (22.6 to 26.9)	19.1 (17.1 to	-5.65 (-8.57 to -2.73)	0.0002[k]
12 weeks	23.4 (21.1 to 25.6)	20.9 (18.9 to	-2.43 (-5.47 to 0.61)	0.1173
PTT, KOA leg[c]				
6 weeks	50.6 (47.6 to 53.5)	45.9 (43.2 to	-4.63 (-8.69 to -0.57)	0.0255[k]
12 weeks	55.9 (52.8 to 59.1)	47.9 (45.1 to	-8.02 (-12.22 to -3.82)	0.0002[k]
PTT, contralateral				
6 weeks	49.6 (47.1 to 52.1)	45.7 (43.4 to	-3.85 (-7.26 to -0.44)	0.0271[k]
12 weeks	52.4 (49.8 to 55.1)	47.4 (45.1 to	-5.03 (-8.56 to -1.50)	0.0053[k]
TS, KOA leg[e]				
6 weeks	1.7 (1.3 to 2.2)	2.1 (1.7 to 2.5)	0.38 (-0.19 to 0.95)	0.1904
12 weeks	1.5 (1.1 to 2.0)	1.5 (1.2 to 1.9)	0.03 (-0.58 to 0.64)	0.9229
CPM, KOA leg[f]				
6 weeks	2.8 (0.1 to 5.4)	3.8 (1.4 to 6.2)	1.03 (-2.52 to 4.58)	0.5694
12 weeks	3.7 (0.9 to 6.5)	3.3 (0.9 to 5.7)	-0.38 (-4.09 to 3.33)	0.8407

[a]Pain pressure threshold in kPa of the most affected leg. [b]Pain pressure threshold in kPa of the least affected leg. [c]Pain tolerance threshold in kPa of the most affected leg. [d]Pain tolerance threshold in kPa of the least affected leg. [e]Temporal summation of pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimuli. [f]The difference in pain pressure thresholds in kPa with and without condition stimuli.

[g]Strength training in addition to neuromuscular exercise and education.

[h]Neuromuscular exercise and education

Table 3 | Knee pain intensity and number of painful body sites at 6- and 12 weeks

Estimated marginal means (95%CI)				
	ST+NEMEX-EDU[c] (n=90)[f]	NEMEX-EDU[d] (n=90)[f]	Adjusted between-group	p
Pain past 24 hours[a]				
6 weeks	38.2 (32.1 to 44.3)	34.6 (29.0 to 40.2)	-3.6 (-11.9 to 4.7)	0.3961
12 weeks	34.5 (28.3 to 40.6)	27.5 (21.8 to 33.2)	-7.0 (-15.4 to 1.4)	0.1011
Pain past week[a]				
6 weeks	42.5 (36.8 to 48.3)	38.4 (33.2 to 43.7)	-4.9 (-11.9 to 3.7)	0.3044
12 weeks	37.9 (32.2 to 43.7)	29.6 (24.2 to 34.9)	-8.4 (-16.2 to -0.5)	0.0364[g]
Pain after 30 min.[a]				
6 weeks	40.8 (34.4 to 47.2)	37.1 (31.2 to 42.9)	-3.8 (-12.5 to 5.0)	0.3985
12 weeks	44.9 (38.5 to 51.4)	28.9 (23.0 to 34.9)	-16.0 (-24.8 to -7.3)	0.0004[g]
Body sites with pain[b]				
6 weeks	3.4 (2.8 to 4.0)	4.1 (3.4 to 4.7)	0.64 (-0.24 to 1.52)	0.1553
12 weeks	3.3 (2.7 to 3.9)	3.4 (2.8 to 4.0)	0.11 (-0.77 to 0.99)	0.8069

[a]Measured on a visual analog scale (VAS) with terminal descriptors of 'no pain' (0mm) and 'worst pain imaginable' (100mm). [b]Number of painful body sites during the last week marked on a region-divided bodychart (21 sites).

[c]Strength training in addition to neuromuscular exercise and education.

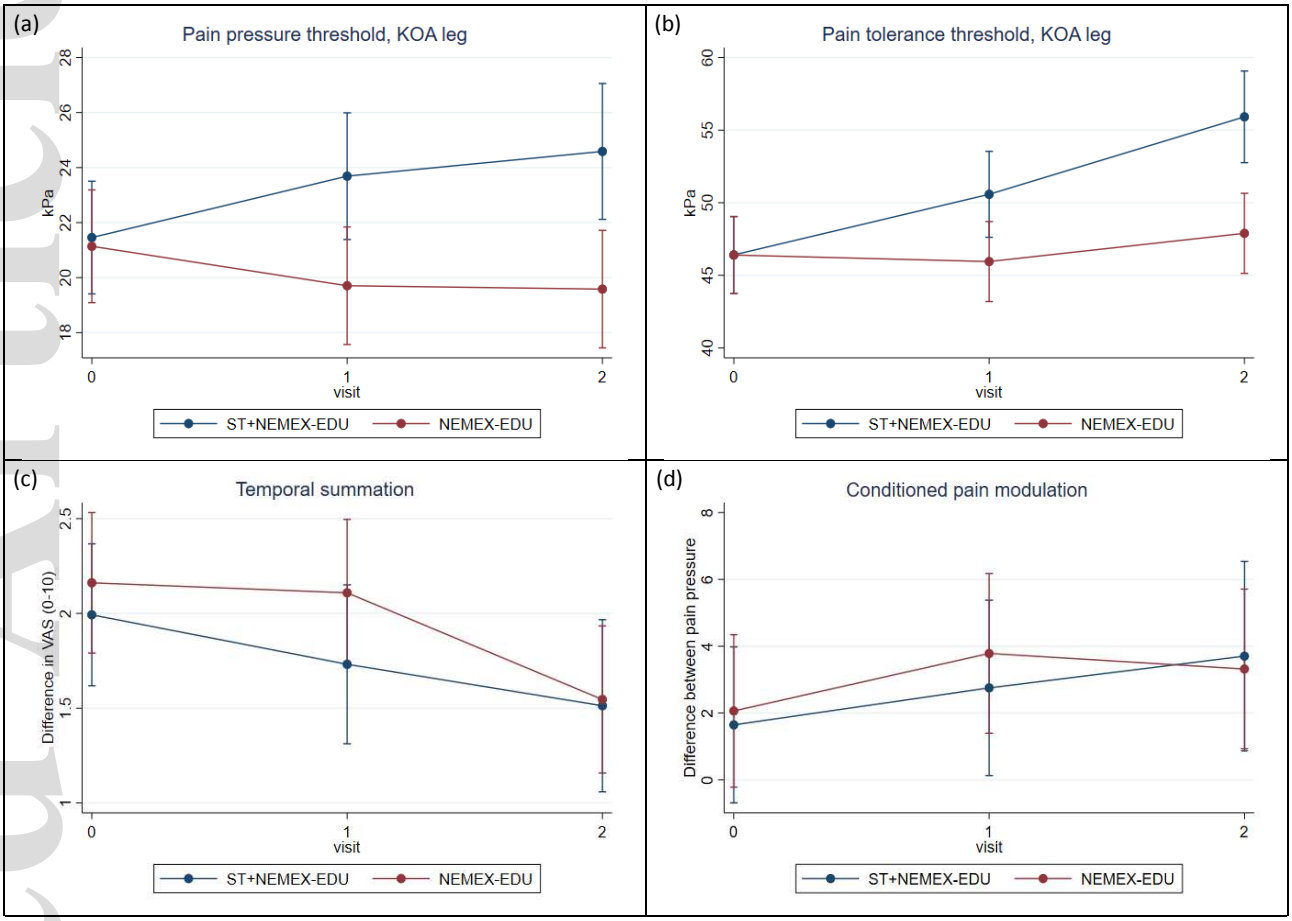
[d]Neuromuscular exercise and education

[e]Adjusted for baseline imbalance.

[f]Analysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the analyses.

[g]$p < 0.05$.

Figure 1 | Quantitative sensory testing of the most symptomatic leg



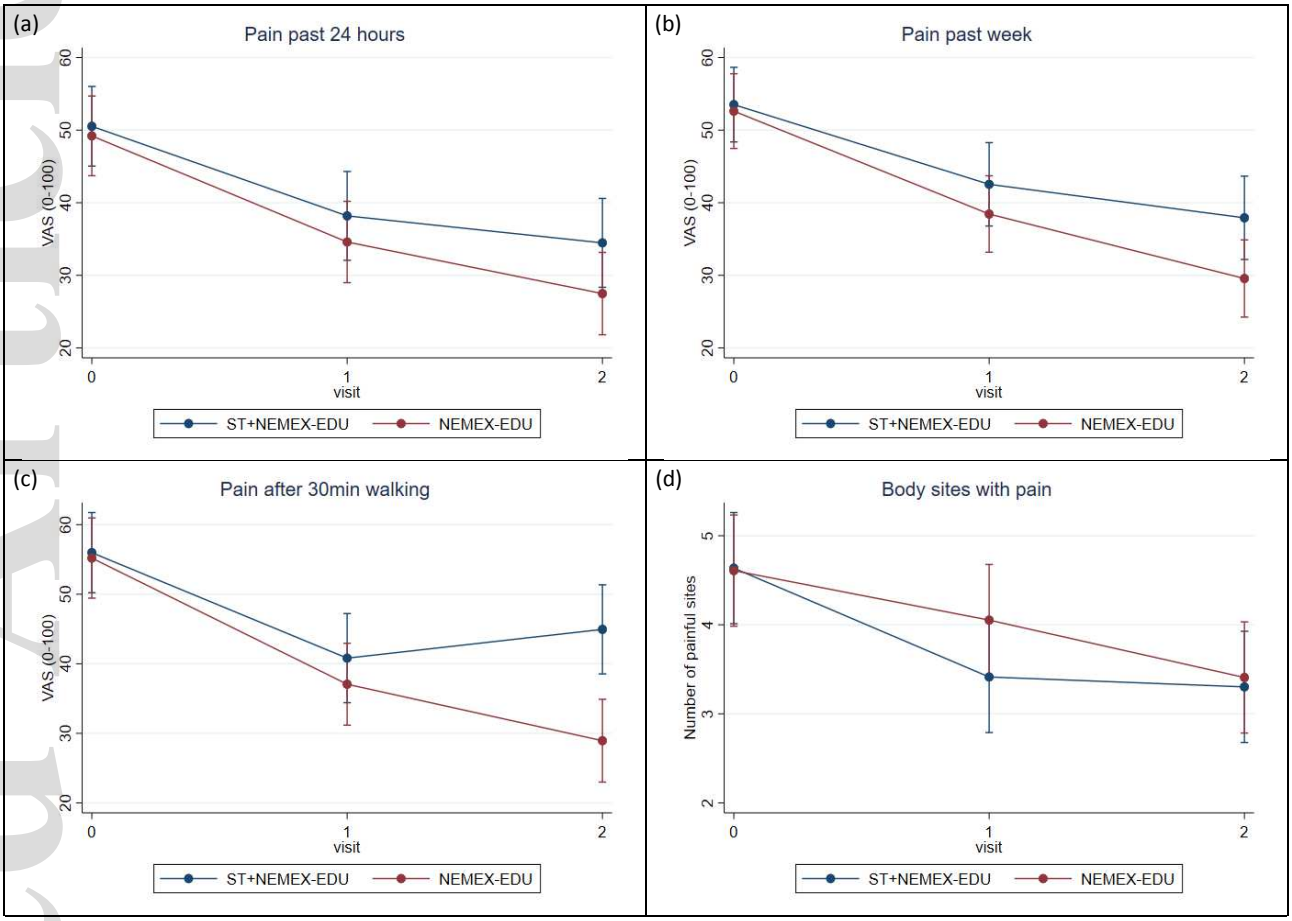
a) Change in pain pressure thresholds (kPa) on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).

b) Change in pain tolerance thresholds (kPa) on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).

c) Change in temporal summation of pain, defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first four of 10 short-lasting (1s) pressure stimul on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).

d) Change in the difference between pain pressure thresholds (kPa) with and without conditioning stimuli on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar).

Figure 2 | Knee pain intensity and number of painful body sites



a) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past 24 hours on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)

b) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past week on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)

c) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) after 30 min walking on the most affected leg from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)

d) Change in the number of painful body sites during the last week marked on a region-divided bodychart (21 sites) from baseline to 6 weeks (visit 1 on x-axis) and 12 weeks (visit 2 on x-axis) for the two groups randomly assigned to strength training in addtion to neuromusucular exercise and education (blue bar) or neuromuscular exercise and education only (red bar)