

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

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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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Title

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

- the effects on pain and sensitization

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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

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Methods

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1 Introduction

2 Knee osteoarthritis (KOA) is a common and disabling condition, particularly in the elderly population
3 with a rising global prevalence partly due to the combined effects of ageing, lifestyle changes and
4 number of joint injuries (GBD 2019 Diseases and Injuries Collaborators, 2020; Hunter and Bierma-
5 Zeinstra, 2019). Pain is the hallmark symptom in KOA (Neogi, 2013) and multiple studies have found
6 localized and widespread hyperalgesia in individuals with KOA compared to non-KOA populations
7 (Arendt-Nielsen et al., 2015a, 2015b; Lluch et al., 2014). Widespread hyperalgesia is most likely a
8 component of generalized sensitization and is believed to be regulated in part by the impacted
9 descending pain inhibition (Arendt-Nielsen et al., 2015b) and described to be impaired in severe
10 chronic pain conditions (Arendt-Nielsen et al., 2018a) including KOA (Arendt-Nielsen et al., 2015a).
11 Temporal summation of pain (TS) is often facilitated in severe KOA (Arendt-Nielsen et al., 2010,
12 2015a; Suokas et al., 2012) and is considered to reflect the process of wind-up in dorsal horn neurons
13 as observed in animals (Arendt-Nielsen and Graven-Nielsen, 2011). Recent evidence suggests that
14 individuals with KOA and generalized sensitization might be more susceptible to worse outcomes (i.e.
15 more pain) following joint replacement surgery (Arendt-Nielsen et al., 2018b; Baert et al., 2016;
16 Petersen et al., 2016), treatment with non-steroidal anti-inflammatory drugs (Arendt-Nielsen et al.,
17 2016; Edwards et al., 2016; Petersen et al., 2019a, 2019b) and exercise therapy (Hansen et al., 2020;
18 O'Leary et al., 2018), indicating that individuals with KOA and pain sensitization might respond less
19 well to standard OA treatment.

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

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

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

48 **Methods**

49 The current study is based on a secondary analysis from a patient-blinded, parallel-group RCT
50 conforming to the CONSORT statement for reporting RCTs (Moher et al., 2010). The primary
51 endpoint of the primary analysis was self-reported physical function after completing 12 weeks of
52 exercise (Holm et al., 2020). Secondary endpoints were after 6 weeks of exercise and 12 months after
53 completion of the exercise program (self-reported only). The 12-month follow-up will be reported
54 independently at later time. The current secondary analysis reports the effects on experimental
55 measures of pain sensitization as well as self-reported knee pain intensity and painful body sites after
56 6- and 12 weeks of exercise, pre-registered with the original registration at ClinicalTrials.gov (ID:
57 NCT03215602).

58 **Ethics**

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

63 **Study population**

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

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

76 Randomization and allocation concealment

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

82 Interventions

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

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

97 Education

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

103 Neuromuscular exercise

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

112 Strength training

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

133 Outcomes

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

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

143 Quantitative sensory testing of pain sensitization

144 The device consisted of a computer-controlled cuff algometer (Cortex Technology, Hadsund and
145 Aalborg University, Aalborg, Denmark) including two 13-cm wide cuffs (VBM, Sulz, Germany) and
146 an electronic Visual Analogue Scale (VAS) (Aalborg University, Aalborg, Denmark) (Petersen et al.,
147 2019a). The computer continuously controlled the compression rate of the cuffs, measured in
148 Kilopascal (kPa). The participants used the electronic VAS to rate the pain intensity to the different
149 pressure stimuli patterns and a button to release the pressure for immediate termination of the cuff
150 pressure. The electronic VAS was sampled at 10 Hz. The VAS pain scale ranged from zero (no pain)
151 to 10 (worst imaginable pain). For safety, the inflation of the cuff could be terminated both
152 mechanically and from the computer program in addition to the pressure release button at the
153 electronic VAS, and the maximal pressure limit was set at 100 kPa.

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

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

162 Cuff pressure pain and tolerance threshold

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

170 Temporal summation

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

181 Conditioned Pain Modulation

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

194 Severity of knee pain and number of painful body sites

195 Knee pain intensity was assessed on a 100mm VAS scale with terminal descriptors of 'no pain'
196 (0mm) and 'worst pain imaginable' (100mm) and patients rated their pain intensity for the following
197 domains; 1. Mean knee pain intensity during the previous 24h; 2. Mean knee pain intensity during the
198 last week; 3. Mean knee pain intensity following 30min. of walking. VAS is a simple, reliable, valid
199 and responsive generic pain measure, applicable across a broad range of populations and settings
200 (Hawker et al., 2011).

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

204 Blinding

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

210 Sample size

211 The sample size was powered for the primary analysis of the RCT and was based on the
212 recommended clinically important difference of 10 points on the KOOS questionnaire (Roos and
213 Lohmander, 2003). With a common standard deviation (SD) of 15 and power of 80% ($\alpha = 0.05$ (two-
214 sided)), 37 participants were required in each group to detect a 10-point between-group difference at
215 12-week follow-up (Roos and Lohmander, 2003). Based on previous studies, this was also deemed
216 sufficient for the purpose of the current study (Henriksen et al., 2014; Tubach et al., 2005).

217 Statistical analysis

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

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

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

233 Results

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

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

331 Comparisons to other randomized controlled trials of therapeutic interventions

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

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

354 Limitations

355 This study has limitations. Firstly, the study sample was powered for the primary RCT. Due to this
356 and to the explorative nature of the analyses, readers should interpret these findings with caution.
357 Secondly, there are some uncertainties regarding reliability and measurement error of the cuff
358 algometer in the assessment of pressure pain and tolerance thresholds (Graven-Nielsen et al., 2015;
359 Imai et al., 2016), which means that we cannot rule out some degree of learning effects for this
360 outcome. The fact that we did not include learning attempts during assessments is a limitation to the
361 interpretation of this outcome. Additionally, we are unaware of established cut-offs for minimal
362 detectable change (MDC) and MID in pain sensitization assessed by cuff pressure algometry. As
363 such, we are unable to infer clinical relevance of the observed differences in PPT and PTT between
364 the two exercise modes. The current study only applied deep pressure stimuli, which has consistently
365 been utilized to assess individuals with OA (Izumi et al., 2017; Kurien et al., 2018; Petersen et al.,
366 2017, 2019a, 2019b), but some studies find thermal changes in patients with OA (Izumi et al., 2017;
367 King et al., 2013; Kuni et al., 2015; Moss et al., 2016) – this was not assessed in the current study and
368 therefore limits the generalizability of our findings. Thirdly, only 19 participants (42%) in the group
369 receiving additional strength training adhered to pre-determined frequencies and intensities (Holm et
370 al., 2020). This is important to consider when interpreting the additional effects of strength training.

371 Conclusion

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

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

380 Author contributions

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

382 Recruitment of patients: Holm, Schrøder

383 Acquisition of data: Holm

384 Analysis and interpretation of data: Holm, Skou

385 Drafting the article or revising it critically for important intellectual content: Holm, Petersen,

386 Wernbom, Schrøder, Arendt-Nielsen, Skou

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

388 All authors had full access to all the data (including statistical reports and tables) in the study and take
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409 Conflicts of interest

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

415 **Tables and figures**

416

417 **Table 1 | Baseline characteristics of participants**

418 **Table legend:**

419 ^aMeasured on a visual analog scale (VAS) with terminal descriptors of ‘no pain’ (0mm) and ‘worst pain imaginable’
420 (100mm). ^bNumber of painful body sites during the last week marked on a region-divided bodychart (21 sites). ^cPain
421 pressure threshold in kPa of the most affected leg. ^dPain pressure threshold in kPa of the least affected leg. ^ePain tolerance
422 threshold in kPa of the most affected leg. ^fPain tolerance threshold in kPa of the least affected leg. ^gTemporal summation of
423 pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final three- and the first
424 four of 10 short-lasting (1s) pressure stimuli. ^hThe difference in pain pressure thresholds in kPa with and without condition
425 stimuli.

426 ⁱStrength training in addition to neuromuscular exercise and education.

427 ^jNeuromuscular exercise and education.

428

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

430 **Table legend:**

431 ^aPain pressure threshold in kPa of the most affected leg. ^bPain pressure threshold in kPa of the least affected leg. ^cPain
432 tolerance threshold in kPa of the most affected leg. ^dPain tolerance threshold in kPa of the least affected leg. ^eTemporal
433 summation of pain on the most affected leg defined as the difference in mean VAS (0-10) pain ratings between the final
434 three- and the first four of 10 short-lasting (1s) pressure stimuli. ^fThe difference in pain pressure thresholds in kPa with and
435 without condition stimuli.

436 ^gStrength training in addition to neuromuscular exercise and education.

437 ^hNeuromuscular exercise and education

438 ⁱAdjusted for baseline imbalance.

439 ^jAnalysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the
440 analyses.

441 ^k $p < 0.05$.

442

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

444 **Table legend:**

445 ^aMeasured on a visual analog scale (VAS) with terminal descriptors of ‘no pain’ (0mm) and ‘worst pain imaginable’
446 (100mm). ^bNumber of painful body sites during the last week marked on a region-divided bodychart (21 sites).

447 ^cStrength training in addition to neuromuscular exercise and education.

448 ^dNeuromuscular exercise and education

449 ^eAdjusted for baseline imbalance.

450 ^fAnalysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the
451 analyses.

452 ^gp <0.05.

453

454 Figure 1 | Quantitative sensory testing of the most symptomatic leg

455 Figure legend:

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

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

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

466 d) Change in the difference between pain pressure thresholds (kPa) with and without conditioning stimuli on the most
467 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
468 assigned to strength training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise
469 and education only (red bar).

470

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

472 Figure legend:

473 a) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past 24
474 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
475 groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or
476 neuromuscular exercise and education only (red bar)

477 b) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) during the past
478 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
479 groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or
480 neuromuscular exercise and education only (red bar)

481 c) Change in knee pain intensity using visual analog scale (VAS), ranging from 0 (best) to 100 (worst) after 30 min
482 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

483 two groups randomly assigned to strength training in addition to neuromuscular exercise and education (blue bar) or
484 neuromuscular exercise and education only (red bar)
485 d) Change in the number of painful body sites during the last week marked on a region-divided bodychart (21 sites) from
486 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
487 training in addition to neuromuscular exercise and education (blue bar) or neuromuscular exercise and education only
488 (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)

^aMeasured on a visual analog scale (VAS) with terminal descriptors of 'no pain' (0mm) and 'worst pain imaginable' (100mm). ^bNumber of painful body sites during the last week marked on a region-divided bodychart (21 sites). ^cPain pressure threshold in kPa of the most affected leg. ^dPain pressure threshold in kPa of the least affected leg. ^ePain tolerance threshold in kPa of the most affected leg. ^fPain tolerance threshold in kPa of the least affected leg. ^gTemporal 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. ^hThe 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 ^c				
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

^aPain pressure threshold in kPa of the most affected leg. ^bPain pressure threshold in kPa of the least affected leg. ^cPain tolerance threshold in kPa of the most affected leg. ^dPain tolerance threshold in kPa of the least affected leg. ^eTemporal 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. ^fThe difference in pain pressure thresholds in kPa with and without condition stimuli.

^gStrength training in addition to neuromuscular exercise and education.

^hNeuromuscular 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

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

^cStrength training in addition to neuromuscular exercise and education.

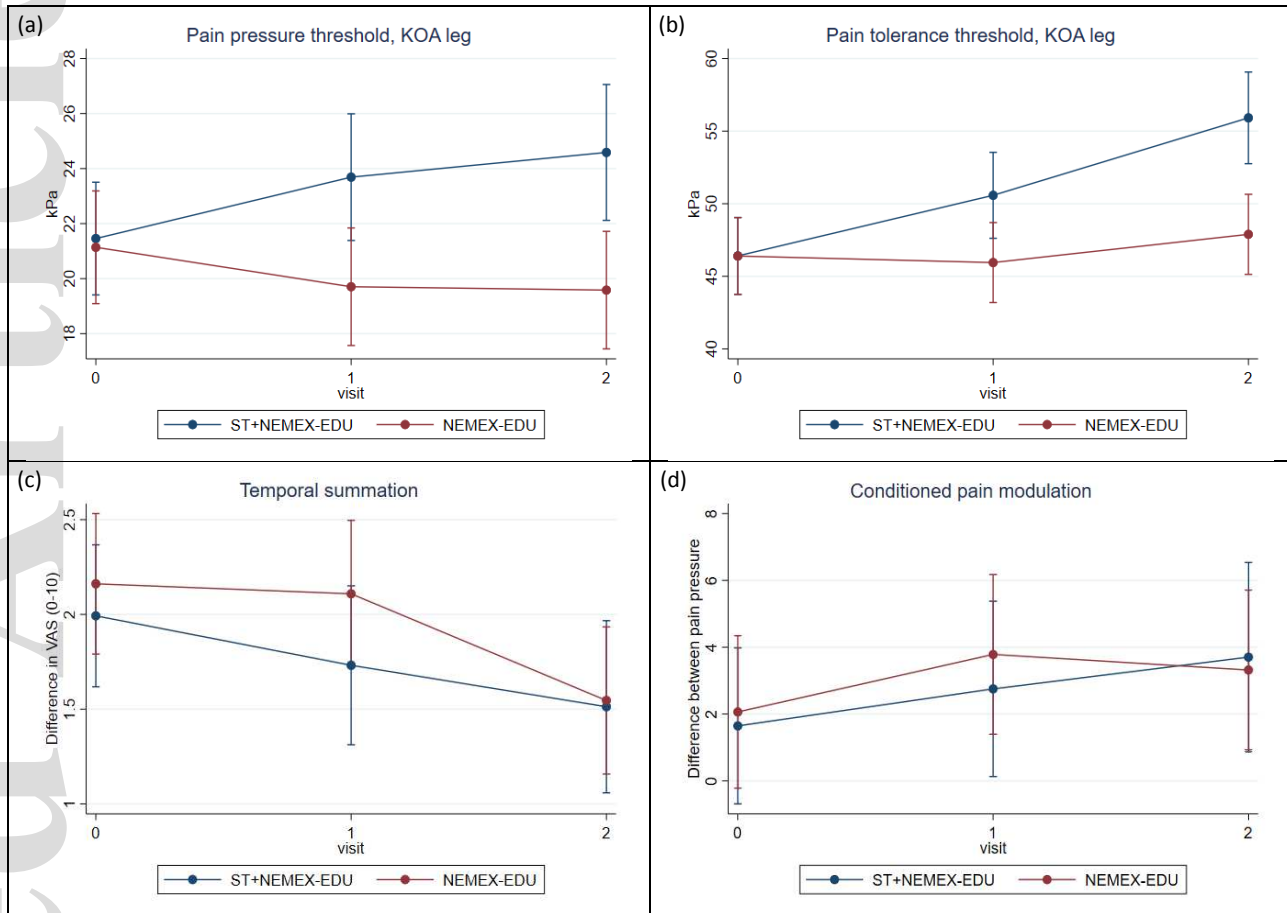
^dNeuromuscular exercise and education

^eAdjusted for baseline imbalance.

^fAnalysed according to the Intention-To-Treat (ITT) principle, meaning that all randomized participants were included in the analyses.

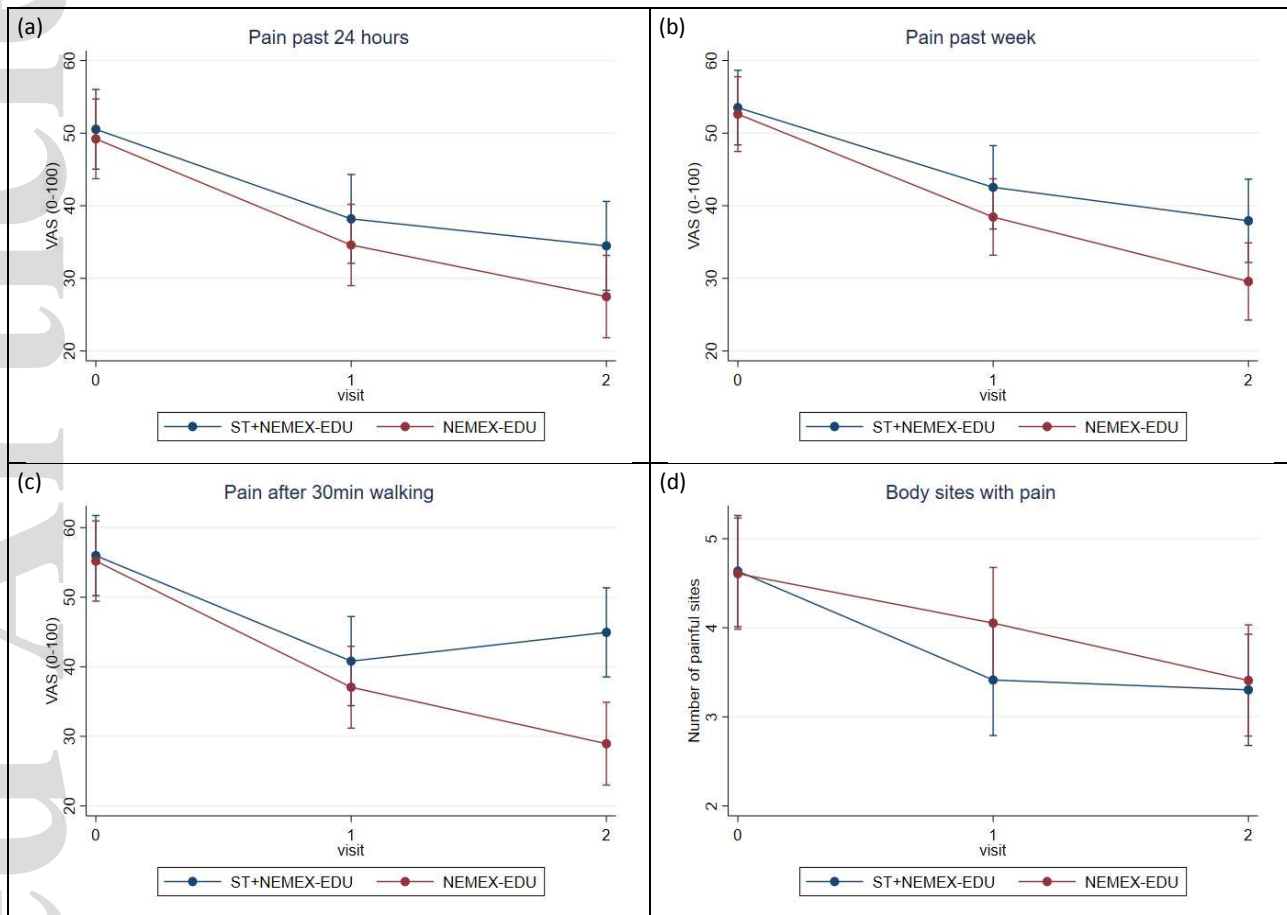
^gp <0.05.

Figure 1 | Quantitative sensory testing of the most symptomatic leg



- 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).
- 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).
- 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 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).
- 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



- 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)
- 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)
- 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)
- 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)